PALM INTRANET

Day : Tuesday
Date: 3/1/2005
Time: 15:50:57

Inventor Name Search Result

Your Search was:

Last Name = SHIRE
First Name = STEVEN

Application#	Patent#	Status	Date Filed	Title	Inventor Name
09705457	Not Issued	061	11/02/2000	TREATING A MAMMAL WITH A FORMULATION COMPRISING AN ANTIBODY WHICH BINDS IGE	SHIRE, STEVEN J,
09638112	6440412	150	08/11/2000	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
09809511	6685940	150	03/14/2001	PROTEIN FORMULATION	SHIRE, STEVEN J.
09971511 1020 ACK Found	Not Issued	094	10/04/2001	REDUCED-VISCOSITY CONCENTRATED PROTEIN FORMULATIONS	SHIRE, STEVEN J.
10076213	Not Issued	061	02/12/2002	DNASE LIQUID SOLUTIONS	SHIRE, STEVEN J.
10155407	Not Issued	092	05/22/2002	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
10428728	Not Issued	071	05/02/2003	PROTEIN FORMULATION	SHIRE, STEVEN J.
10813483	Not Issued	071	03/29/2004	HIGH CONCENTRATION ANTIBODY AND PROTEIN FORMULATIONS	SHIRE, STEVEN J.
10826797	Not Issued	030	04/16/2004	METHOD FOR TREATMENT OF ALLERGIC ASTHMA	SHIRE, STEVEN J.
60240107	Not Issued	159	10/12/2000	REDUCED VISCOSITY CONCENTRATED PROTEIN FORMULATIONS	SHIRE, STEVEN J.
60293834	Not Issued	159	05/24/2001	REDUCED VISCOSITY CONCENTRATED PROTEIN FORMULATIONS	SHIRE, STEVEN J.
60460659 prov	Not Issued	159	04/04/2003	HIGH CONCENTRATION ANTIBODY AND PROTEIN FORMULATIONS	SHIRE, STEVEN J.
06452253	Not Issued	166	12/22/1982	PURIFICATION AND ACTIVITY ASSURANCE OF	SHIRE, STEVEN J.

				PRECIPITATED HETEROLOGOUS PROTEINS	
06615679	4512922	150	06/01/1984	PURIFICATION AND ACTIVITY ASSURANCE OF PRECIPITATED HETEROLOGOUS PROTEINS	SHIRE, STEVEN J.
07160797	Not Issued	168	02/26/1988	HUMAN RELAXIN FORMULATION	SHIRE, STEVEN J.
07303779	Not Issued	166	01/27/1989	HUMAN RELAXIN FORMULATION	SHIRE, STEVEN J.
07895300	5279823	150	06/08/1992	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
08050745	5451572	150	04/20/1993	HUMAN RELAXIN FORMULATION	SHIRE, STEVEN J.
08116186	Not Issued	166	09/02/1993	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
08206020	Not Issued	166	03/04/1994	PHARMACEUTICALLY ACCEPTABLE DNASE FORMULATION	SHIRE, STEVEN J.
08348284	Not Issued	166	11/30/1994	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
08364074	Not Issued	163	12/27/1994	PHARMACEUTICALLY ACCEPTABLE DNASE FORMULATION	SHIRE, STEVEN J.
08409631	Not Issued	166	03/22/1995	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
08471920	5945402	150	06/06/1995	HUMAN RELAXIN FORMULATION	SHIRE, STEVEN J.
08508014	Not Issued	168	07/27/1995	METHODS FOR TREATING OF ALLERGIC ASTHMA	SHIRE, STEVEN J.
08615369	6267958	150	03/14/1996	PROTEIN FORMULATION	SHIRE, STEVEN J.
08634125	Not Issued	166	04/19/1996	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
08686902	Not Issued	161	07/26/1996	METHOD FOR TREATMENT OF ALLERGIC ASTHMA	SHIRE, STEVEN J.
08696955	6383788	150	12/03/1996	MINIMIZING THERMALLY INDUCED AGGREGATION OF DNASE IN SOLUTION WITH CALCIUM	SHIRE, STEVEN J.
08942561	Not Issued	161	10/01/1997	PURIFIED FORMS OF DNASE	SHIRE, STEVEN J.
60029182	Not Issued	159	07/27/1995	METHODS FOR TREATMENT OF ALLERGIC ASTHMA	SHIRE, STEVEN J.

07766726	5220167	150	09/27/1991	MULTIPLE ION MULTIPLIER DETECTOR FOR USE IN A MASS SPECTROMETER	SHIREY, STEVEN B.

Inventor Search Completed: No Records to Display.

Search Another: Inventor **Last Name** shire **First Name** steven Search

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Day : Tuesday
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Inventor Name Search Result

Your Search was:

Last Name = LIU
First Name = JUN

Application#	Patent#	Status	Date Filed	Title	Inventor Name
07127196	4917711	150	12/01/1987	NOVEL ADSORBENTS FOR USE IN THE SEPARATION OF CARBON MONOXIDE AND/OR UNSATURATED HYDROCARBONS FROM MIXED GASES	LIU, JUN
07740175	5362629	150	08/05/1991	DETECTION OF IMMUNOSUPPRESSANTS	LIU, JUN
07868145	5322601	150	04/14/1992	AMPEROMETRIC GAS SENSOR TO SELECTIVELY DETERMINE THE PARTIAL PRESSURES OF A GAS	LIU, JUN
07868159	Not Issued	161	04/14/1992	REFERENCE ELECTRODE, ITS APPLICATION IN GAS SENSORS WITH SOLID ELECTROLYTES, AND GAS SENSORS CONTAINING SUCH ELECTRODES	LIU, JUN
08328077	5585792	150	10/24/1994	ENERGY-SAVING KEYBOARD	LIU, JUN
08344330	5645891	150	11/23/1994	CERAMIC POROUS MATERIAL AND METHOD OF MAKING SAME	LIU, JUN
08522620	5599851	150	09/01/1995	SUPERFINE MICROELEMENTAL BIOCHEMICAL MIXTURE AND FOAMED PLASTIC PRODUCTS THEREOF	LIU, JUN
08537784	5814488	150	01/05/1996	SEMISYNTHETIC 1-N-ETHYL GENTAMICIN C1A AND METHOD FOR ITS PREPARATION	LIU, JUN
08617313	5751189	150	03/18/1996	CHARGE AMPLIFIER FOR MOS IMAGING ARRAY AND METHOD OF MAKING SAME	LIU, JUN

08753573	Not Issued	168	11/26/1996	MESOPOROUS-SILICA FILMS, FIBERS, AND POWDERS BY EVAPORATION	LIU, JUN
08753588	Not Issued	169	11/26/1996	CHARGE AMPLIFIER FOR MOS IMAGING ARRAY	LIU, JUN
08755576	6351283	150	11/27/1996	CHARGE AMPLIFIER FOR MOS IMAGING ARRAY	LIU, JUN
08785247	6040149	150	01/10/1997	ASSAY FOR IDENTIFYING AGENTS WHICH ACT ON THE CERAMIDE-ACTIVATED PROTEIN KINASE, KINASE SUPPRESSOR OF RAS, AND METHODS OF USING SAID AGENTS	LIU, JUN
08796352	Not Issued	161	02/07/1997	SURFACE FUNCTIONALIZED MESOPOROUS MATERIAL AND METHOD OF MAKING SAME	LIU, JUN
08845674	5928868	150	04/25/1997	THREE HYBRID SCREENING ASSAY	LIU, JUN
08907431	5795836	150	08/07/1997	MEDICAL NON-WOVEN FABRICS CONTAINING INORGANIC OXIDES COMPLEX POWDER	LIU, JUN
08921754	5922299	150	08/26/1997	MESOPORUS-SILICA FILMS, FIBERS, AND POWDERS BY EVAPORATION	LIU, JUN
08938228	6129973	150	09/26/1997	MICROCHANNEL LAMINATED MASS EXCHANGER AND METHOD OF MAKING	LIU, JUN
09020028	6326326	150	02/06/1998	SURFACE FUNCTIONALIZED MESOPOROUS MATERIAL AND METHOD OF MAKING SAME	LIU, JUN
09036363	5997961	150	03/06/1998	METHOD OF BONDING FUNCTIONAL SURFACE MATERIALS TO SUBSTRATES AND APPLICATIONS IN MICROTECHOLOGY AND ANTIFOULING	LIU, JUN
09157542	Not Issued	161	09/21/1998	1-N-ETHYL GENTAMICIN DERIVATIVES AND THE METHOD FOR PREPARING THEREOF	LIU, JUN
09220882	Not Issued	168	12/23/1998	METHOD OF MAKING A MESOPOROUS FILM	LIU, JUN
09222569	6383466	150	12/28/1998	METHOD OF DEHYDROXYLATING A	LIU, JUN

				HYDROXYLATED MATERIAL AND METHOD OF MAKING A MESOPOROUS FILM	
09236360	6345319	150	01/25/1999	METHOD FOR INSTALLING PLUG-N-PLAY DEVICE BY COPYING INF FILES TO A CORRESPONDING DIRECTORY AND DELETING DEVICE ID AND ALL RELATED DEVICE CLASS OF AN ORIGINAL DEVICE	LIU, JUN
09255364	6412080	150	02/23/1999	LIGHTWEIGHT PERSISTENT STORAGE SYSTEM FOR FLASH MEMORY DEVICES	LIU, JUN
09272762	Not Issued	161	03/19/1999	SELF-ASSEMBLED MONOLAYER AND METHOD OF MAKING	LIU, JUN
09333876	6361861	150	06/14/1999	CARBON NANOTUBES ON A SUBSTRATE	LIU, JUN
09335210	Not Issued	168	06/17/1999	MESOPOROUS SILICA FILM FROM A SOLUTION CONTAINING A SURFACTANT AND METHODS OF MAKING SAME	LIU, JUN
09348387	6321223	150	07/07/1999	METHOD OF IDENTIFYING MULTILINGUAL TEXT FOR DOS	LIU, JUN
09361499	Not Issued	168	07/23/1999	MESOPOROUS SILICA FILM FROM A SOLUTION CONTAINING A SURFACTANT AND METHODS OF MAKING SAME	LIU, JUN
09371419	6775713	150	08/10/1999	APPLICATION PROGRAM INTERFACE FOR ABSTRACTING CONTROL OF A CABLE MODEM	LIU, JUN
09371914	6618386	150	08/10/1999	HOSTING A CABLE MODEM IN A COMPUTER USING A VIRTUAL BRIDGE	LIU, JUN
09371915	6618387	150	08/10/1999	INTERFACE FOR ABSTRACTING CONTROL OF A CABLE MODEM	LIU, JUN
09371916	Not Issued	094	08/10/1999	AUTOMATIC COMPILING OF ADDRESS FILTER INFORMATION	LIU, JUN
09410173	6270903	150	09/30/1999	METHOD OF BONDING	LIU, JUN

				FUNCTIONAL SURFACE MATERIALS TO SUBSTRATES AND APPLICATIONS IN MICROTECHNOLOGY AND ANTIFOULING	
09411360	Not Issued	168	10/01/1999	METAL OXIDE STABILIZED TIO2 ANATASE NANOCRYSTALLITES IN A MESOPOROUS STRUCTURE	LIU, JUN
09413062	6329017	150	10/04/1999	MESOPOROUS SILICA FILM FROM A SOLUTION CONTAINING A SURFACTANT AND METHODS OF MAKING SAME	LIU, JUN
09481988	Not Issued	133	01/11/2000	MESOPOROUS-SILICA FILMS, FIBERS, AND POWDERS BY EVAPORATION	LIU, JUN
09525553	Not Issued	161	03/15/2000	CHEMICAL-SENSORS BASED ON DIELECTRIC RESPONSE OF MESOPOROUS FILMS	LIU, JUN
09560838	Not Issued	041	04/28/2000	COMPRESSED FILE SYSTEM FOR NON-VOLATILE RAM	LIU, JUN
09560857	6683630	150	04/28/2000	METHODS AND ARRANGEMENTS FOR ALLOWING INDEPENDENT PROGRAMS MODULES TO ACCESS SHARED DISPLAY DEVICE RESOURCES	LIU, JUN
09564476	6352577	150	05/03/2000	MICROCHANNEL LAMINATED MASS EXCHANGER AND METHOD OF MAKING	LIU, JUN
09584130	6382836	150	05/31/2000	ROLLING BEARING	LIU, JUN
09682850	Not Issued	041	10/24/2001	AUTOMATED REPETITIVE ARRAY MICROSTRUCTURE DEFECT INSPECTION	LIU, JUN
09749430	Not Issued	071	12/28/2000	INTERNET BACKBONE PACKET RADIO	LIU, JUN
09750043	Not Issued	041	12/29/2000	METHOD FOR PURCHASES THROUGH A NETWORK	LIU, JUN
09755874	Not Issued	083	01/05/2001	METHODS AND ARRANGEMENTS FOR MANAGING DEVICES	LIU, JUN
09756052	Not Issued	083	01/05/2001	METHODS AND ARRANGEMENTS FOR PROVIDING IMPROVED	LIU, JUN

				SOFTWARE VERSION CONTROL IN MANAGED DEVICES	
09791138	Not Issued	041	02/21/2001	PROTEINS IN A POROUS SUPPORT	LIU, JUN
09798603	Not Issued	161	03/02/2001	HYBRID POROUS MATERIALS FOR CONTROLLED RELEASE	LIU, JUN

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TYPE S15/MEDIUM,AB/1-5

15/AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014724748 BIOSIS NO.: 200400093517
Influence of histidine on the stability and physical properties of a fully human antibody in aqueous and solid forms.
AUTHOR: Chen Bei (Reprint); Bautista Raquel; Yu Kwok; Zapata Gerardo A; Mulkerrin Michael G; Chamow Steven M
AUTHOR ADDRESS: Department of Process Sciences, Abgenix, Inc., Fremont, CA, 94555, USA**USA
AUTHOR E-MAIL ADDRESS: Bei.Chen@abgenix.com
JOURNAL: Pharmaceutical Research (Dordrecht) 20 (12): p1952-1960 December 2003 2003
MEDIUM: print
ISSN: 0724-8741 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: The aim of the study was to investigate the effect of histidine on the stability and physical properties of a fully human anti-IL8 monoclonal antibody (ABX-IL8) in aqueous and solid forms. Method: Using a fractional factorial design, we tested many excipients, including histidine, sucrose, and other commonly used excipients, on the stability and physical properties of the antibody in both liquid and lyophilized forms. Antibody stability and physical properties were evaluated using size-exclusion high-performance liquid chromatography (SEC-HPLC), sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and a viscometer. Residual moisture content was determined by coulometric Karl Fischer titrator. Differential scanning calorimetry (DSC) was used to detect the glass transition temperatures (Tg) of the solid cakes and melting temperatures (Tm) of the antibody in liquid formulations. Fourier-transform infrared (FTIR) spectroscopy was used to examine the overall secondary structure. Results: Increasing the histidine concentration in the bulk solution inhibited the increases of high-molecular-weight (HMW) species and aggregates upon lyophilization and storage. In addition, histidine bulk enhanced solution stability of the antibody under freezing and thermal stress conditions, as evidenced by the lower levels of aggregates. Furthermore, histidine reduced viscosity of the antibody solution, which is desirable for the manufacture of the dosage form. However, high concentrations of histidine in liquid formulations led to coloration of the solution and high levels of aggregates on storage at elevated temperature (40degreeC) after the formulations were exposed to stainless steel containers during bulk freezing-thawing. Conclusions: Histidine enhanced the stability of ABX-IL8 in both aqueous and lyophilized forms. Histidine also improved the physical properties such as reducing the solution viscosity. Liquid formulations containing high concentrations of histidine should not be stored in stainless steel tanks at elevated temperatures.

15/AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010671897 BIOSIS NO.: 199799305957
The effect of sugars and buffer excipients on the stabilization of a

lyophilized formulation for an anti-IgE humanized monoclonal antibody
AUTHOR: Andya James; Wu Sylvia; Hsu Chung; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Research Development, Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.): pS78 1996 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996; 19961027
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

15/AB/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07183819 EMBASE No: 1998050426
Chicken antibodies to a recombinant fragment of the equine immunoglobulin epsilon heavy-chain recognizing native horse IgE
Marti E.; Peveri P.; Griot-Wenk M.; Muntwyler J.; Crameri R.; Schaller J.; Gerber H.; Lazary S.
E. Marti, Division of Immunogenetics, Institute of Animal Breeding, Bremgartenstr. 109A, CH 3012 Berne Switzerland
AUTHOR EMAIL: marti@itz.unibe.ch
Veterinary Immunology and Immunopathology (VET. IMMUNOL. IMMUNOPATHOL.) (Netherlands) 1997, 59/3-4 (253-270)
CODEN: VIIMD ISSN: 0165-2427
PUBLISHER ITEM IDENTIFIER: S0165242797000962
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 27

An equine immunoglobulin E (IgE) heavy-chain cDNA fragment (CH3-CH4, nucleotides 1132 to 1592) was cloned, expressed in Escherichia coli as a fusion protein with a (His)inf 6-tag and purified over a Ni-NTA column. The recombinant protein was used to immunise hens. Testing of the raised egg yolk immunoglobulin G (IgG) in Western-blot and ELISA revealed high titres against the recombinant equine IgE fragment (reqIgEf). The reqIgEf-specific IgG was successfully affinity-purified on an unconventional affinity matrix: the (His)inf 6-tagged recombinant IgE fragment was bound to Ni-NTA agarose and used to adsorb specific immunoglobulins. In Western-blot of ammonium sulphate precipitated horse serum and bronchoalveolar lavage fluid, separated by SDS- PAGE under denaturing-reducing conditions, the raised antibodies reacted with a protein of approximately 80 kDa. A reaction of the reqIgEf-specific IgG was seen with a 190-200 kDa band when the same horse serum or bronchoalveolar fluid (BALF) was separated under non-reducing conditions. These reactions could be inhibited by preincubation of the immune IgG with reqIgEf, while preincubation with horse IgG did not inhibit the reaction. Antibody-affinity chromatography of horse serum with the reqIgEf-specific chicken IgG resulted in an enrichment of the 80 kDa protein in denaturing Western-blot. Determination of the amino acid composition of this protein and comparison with the equine IgE heavy- chain sequence strongly indicates that the 80 kDa band corresponds to the heavy chain of the horse IgE. The reqIgEf-specific chicken IgG was further characterized in an ELISA for the detection of allergen-specific horse IgE. It was demonstrated that heating IgE positive horse sera at 54degreeC for 10 min drastically diminished the recognition by the reqIgEf-specific chicken IgG. The reaction is inhibitable by preincubation

with reqIgEf in a concentration dependent manner. In addition, preincubation with horse IgG, a nonrelevant (His)inf 6-tagged protein or 2% equine colostrum had no influence on the reqIgEf-specific chicken IgG binding characteristic. This antibody recognizing horse IgE will be useful for further studies on the pathogenesis of equine allergic diseases.
?

Set	Items	Description
S1	1974216	ANTIBOD?
S2	354869	VACCINE?
S3	2215611	S1 OR S2
S4	1425599	COMPOSITION?
S5	276632	FORMULAT?
S6	1688551	S4 OR S5
S7	44026	S3 AND S6
S8	234	S7 AND ARGININE
S9	195	S7 AND HISTIDINE
S10	398	S8 OR S9
S11	3	S10 AND VISCOSITY
S12	1597321	11
S13	2	S10 AND IGE
S14	5	S11 OR S13
S15	3	RD S14 (unique items)

?

TYPE S4/MEDIUM,AB/1-19

4/AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015155008 BIOSIS NO.: 200500062073
Gene cloning and tissue expression analysis of a PR-5 thaumatin-like protein in Phellinus weirii-infected Douglas-fir
AUTHOR: Zamani Arezoo; Sturrock Rona N; Ekramoddoullah Abul K M (Reprint); Liu Jun Jun; Yu Xueshu
AUTHOR ADDRESS: Nat Resources Canada, Canadian Forestry Serv, 506 W Burnside Rd, Victoria, BC, V8Z 1M5, Canada**Canada
AUTHOR E-MAIL ADDRESS: aekramod@pfc.cfs.nrcan.gc.ca
JOURNAL: Phytopathology 94 (11): p1235-1243 November 2004 2004
MEDIUM: print
ISSN: 0031-949X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In western North America, Douglas-fir (Pseudotsuga menziesii) is the most economically important conifer species susceptible to laminated root rot caused by Phellinus weirii. While attempting to internally sequence an endochitinase found to be up-regulated in P. weirii-infected Douglas-fir roots, we obtained overlapping peptide fragments showing 28% similarity with a PR-5 thaumatin-like protein (TLP) designated PmTLP (Pm for Pseudotsuga menziesii). A rabbit polyclonal antibody was reared against a synthetic peptide composed of a 29-amino-acid-long, conserved, internal sequence of PmTLP and purified by immunoaffinity. Western immunoblot analysis of infected roots of 24-year-old coastal Douglas-fir showed significantly higher amounts of PmTLP ($P < 0.01$) closest to the point of P. weirii inoculation and infection than in uninfected regions of the same root. The antibody was also used to screen for PmTLP in roots of 25-year-old interior Douglas-firs naturally infected with a related pathogen, Armillaria ostoyae, and results showed significantly higher levels of PmTLP in bark tissues adjacent to infection ($P < 0.05$) than in uninfected tissue. Using polymerase chain reaction (PCR)based cloning, the cDNA of PmTLP was shown to have a 702-bp open reading frame with a signal peptide cleavage site at 155 bp corresponding to a 29-amino-acid-long residue prior to the start of the N-terminal. Based on the deduced amino acid sequence, the molecular mass of the putative PmTLP was calculated to be 21.0 kDa with an isoelectric point of 3.71. Alignment analysis of PmTLP cDNA with a representative genomic DNA PCR sequence showed presence of one intron of variable size, within the coding region. The induction of PmTLP at the site of root infection and its presence in needle tissue suggests a general role for this protein in adaptation to stress and may be part of an integrated defense response initiated by the host to impede further pathogen spread.

4/AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014417694 BIOSIS NO.: 200300376413
Full length cDNA cloning and tissue expression specificity of Ran gene in color crucian carp.
AUTHOR: Li Chang-Jian; Liu Jun; Shi Yao-Hua; Yang Shu-Ting; Gui Jian-Fang (Reprint)

AUTHOR ADDRESS: State Key Laboratory of Freshwater Ecology and Biotechnology, Institute of Hydrobiology, Chinese Academy of Sciences, Wuhan, 430072, China**China
AUTHOR E-MAIL ADDRESS: jfgui@ihb.ac.cn
JOURNAL: Zoological Research 24 (3): p173-179 Jun. 2003 2003
MEDIUM: print
ISSN: 0254-5853
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Chinese

ABSTRACT: A full-length cDNA of Ran gene was cloned from color crucian carp (Carassius auratus color variety) by using SMART cDNA synthesis and RACE-PCR with a pair of degenerate primers designed according to the conserved region sequence of Ran gene. The Ran cDNA was found to be 1 081 bp in length with a 67 bp 5'UTR and a 366 bp 3' UTR. The coding region included 648 nucleotide acids and encoded 215 amino acids. Searching homologous genes by using this nucleotide sequence in NCBI database showed that the deduced amino acids sequence of Ran gene of color crucian carp shared high identity with Ran genes of Dano rerio (98%) and Salmo salar (97%). Moreover, the full-length sequence of its coding region was expressed in E. coli (DE3). To acquire multiclonal antibody, the expressed protein was purified and applied to immunize rabbits. Western blotting results indicated that the multiclonal antibody prepared by us was highly specific to recognize Ran proteins expressed in E. coli or that from eggs of color crucian carp. In addition, analysis on tissue expression specificity indicated that Ran protein was expressed in ovary, testis and kidney, whereas was not detected in heart, brain, liver, spleen and muscle. The present studies will facilitate our future studies on the physiological functions of Ran gene, the isolation and identification of its binding proteins in fish by using immunodepletion, coimmunoprecipitation, and simulative systems in vitro.

4/AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014305775 BIOSIS NO.: 200300264419
Design, construction, and in vitro analyses of multivalent antibodies.
AUTHOR: Miller Kathy (Reprint); Meng Gloria; Liu Jun; Hurst Amy; Hsei Vanessa; Wong Wai-Lee; Ekert Rene; Lawrence David; Sherwood Steven; Deforge Laura; Gaudreault Jacques; Keller Gilbert; Sliwkowski Mark; Ashkenazi Avi; Presta Leonard
AUTHOR ADDRESS: DNAX Research Institute, 901 California Avenue, Palo Alto, CA, 94304-1104, USA**USA
AUTHOR E-MAIL ADDRESS: kathy.miller6@dnax.org
JOURNAL: Journal of Immunology 170 (9): p4854-4861 May 1, 2003 2003
MEDIUM: print
ISSN: 0022-1767 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Some Abs are more efficacious after being cross-linked to form dimers or multimers, presumably as a result of binding to and clustering more surface target to either amplify or diversify cellular signaling. To improve the therapeutic potency of these types of Abs, we designed and generated Abs that express tandem Fab repeats with the aim of mimicking cross-linked Abs. The versatile design of the system enables the creation

of a series of multivalent human IgG Ab forms including tetravalent IgG1, tetravalent F(ab')2, and linear Fab multimers with either three or four consecutively linked Fabs. The multimerized Abs target the cell surface receptors HER2, death receptor 5, and CD20, and are more efficacious than their parent mAbs in triggering antitumor cellular responses, indicating they could be useful both as reagents for study as well as novel therapeutics.

4/AB/4 (Item 4 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

0013116573 BIOSIS NO.: 200100288412

High expression in CHO cells and activity of an anti-P185erbB2 mouse/human chimeric antibody

AUTHOR: Yang Guang; Ran Yu-liang; Sun Li-Xin; Liu Jun; Yu Long; Yang Zhi-Hua (Reprint)
AUTHOR ADDRESS: Department of Cellular and Molecular Biology, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, 100021, China** China

JOURNAL: Shengwu Huaxue yu Shengwu Wuli Xuebao 33 (1): p87-92 2001 2001
MEDIUM: print
ISSN: 0582-9879
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Chinese

ABSTRACT: The McAb C25 against human P185erbB2 specifically inhibits proliferation of cancer cells overexpressing P185erbB2. In order to decrease HAMA response in clinical therapy of human cancer using McAb, and to express this antibody efficiently in CHO cells, an anti-P185erbB2 mouse/human chimeric antibody gene containing variable region of C25 gene was constructed. The expression vectors were constructed using genomic DNA of human IgG1 constant region, and using neo and dhfr genes driven by weaker promoters as selectable marker genes. Variable region genes of C25 were cloned by RT-PCR. VL and VH genes of C25 were sequenced and then inserted, respectively, into the light chain and heavy chain expression vectors. The two expression vectors were cotransfected into CHO-dhfr- cells with LipofectAMINE. The specificity of the chimeric antibody was verified using cellular-ELISA and immuno-fluorescence techniques. ELISA and RT-PCR were used to confirm that the chimeric antibody containing both variable region of C25 and human constant region. At 72 h post-transfection, the chimeric antibody could be detected in supernatant of CHO cells by ELISA assay and the yield was 1 mg/L. After the selection by G418, stepwise MTX pressure (1 X 10-8 dollar sign2.5 X 10-7 mol/L) culture was carried out, and the yield of the chimeric antibody was increased up to 100 mg/L. The chimeric antibody was demonstrated to have the antigen specificity to P185erbB2 and to carry the human antibody constant region by cellular-ELISA, immuno- fluorescence assay, indirect-ELISA and RT-PCR. The chimeric antibody could inhibit proliferation of SKBR3 and SKOV3 cells at the same inhibiting rate as McAb C25. In conclusion, a mouse/human chimeric antibody against human P185erbB2 with potential of usage in clinical therapy of human cancer was constructed and highly expressed.

4/AB/5 (Item 5 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

0013086191 BIOSIS NO.: 200100258030
An RGD sequence in the P2Y2 receptor interacts with alphaVbeta3 integrins and is required for Go-mediated signal transduction
AUTHOR: Erb Laurie (Reprint); Liu Jun; Ockerhausen Jonathan; Kong Qiongman; Garrad Richard C; Griffin Korey; Neal Chris; Krugh Brent; Santiago-Perez Laura I; Gonzalez Fernando A; Gresham Hattie D; Turner John T; Weisman Gary A
AUTHOR ADDRESS: Department of Biochemistry, University of Missouri-Columbia, M121 Medical Science Building, Columbia, MO, 65212, USA**USA
JOURNAL: Journal of Cell Biology 153 (3): p491-501 April 30, 2001 2001
MEDIUM: print
ISSN: 0021-9525
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The P2Y2 nucleotide receptor (P2Y2R) contains the integrin-binding domain arginine-glycine-aspartic acid (RGD) in its first extracellular loop, raising the possibility that this G protein-coupled receptor interacts directly with an integrin. Binding of a peptide corresponding to the first extracellular loop of the P2Y2R to K562 erythroleukemia cells was inhibited by antibodies against alphaVbeta3/beta5 integrins and the integrin-associated thrombospondin receptor, CD47. Immunofluorescence of cells transfected with epitope-tagged P2Y2Rs indicated that alphaV integrins colocalized 10-fold better with the wild-type P2Y2R than with a mutant P2Y2R in which the RGD sequence was replaced with RGE. Compared with the wild-type P2Y2R, the RGE mutant required 1,000-fold higher agonist concentrations to phosphorylate focal adhesion kinase, activate extracellular signal-regulated kinases, and initiate the PLC-dependent mobilization of intracellular Ca2+. Furthermore, an anti-alphaV integrin antibody partially inhibited these signaling events mediated by the wild-type P2Y2R. Pertussis toxin, an inhibitor of Gi/o proteins, partially inhibited Ca2+ mobilization mediated by the wild-type P2Y2R, but not by the RGE mutant, suggesting that the RGD sequence is required for P2Y2R-mediated activation of Go, but not Gq. Since CD47 has been shown to associate directly with Gi/o family proteins, these results suggest that interactions between P2Y2Rs, integrins, and CD47 may be important for coupling the P2Y2R to Go.

4/AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012471839 BIOSIS NO.: 200000190152
Self-association of rhuMAb VEGF occurs via a Fab:Fab interaction
AUTHOR: Cromwell Mary E M (Reprint); Patapoff Thomas (Reprint); Moore Jamie (Reprint); Liu Jun (Reprint)
AUTHOR ADDRESS: Pharmaceutical R and D, Genentech, Inc, 1 DNA Way, South San Francisco, CA, 94080-4918, USA**USA
JOURNAL: Abstracts of Papers American Chemical Society 219 (1-2): pBIOT 186 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 219th Meeting of the American Chemical Society. San Francisco, California, USA March 26-30, 2000; 20000326
SPONSOR: American Chemical Society
ISSN: 0065-7727

DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011861333 BIOSIS NO.: 199900120993
Preliminary studies on pharmacological actions of Tongcao and Xiao-Tongcao polysaccharides
AUTHOR: Shen Yingjun; Zeng Nan; Liu Jun; Jia Minru; Zhang Yi; Wei Yingfang; Ma Yuyin
AUTHOR ADDRESS: Chengdu Univ. TCM, Chengdu 610075, China**China
JOURNAL: Zhongguo Zhongyao Zazhi 23 (12): p741-743, 765 Dec., 1998 1998
MEDIUM: print
ISSN: 1001-5302
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Chinese

ABSTRACT: Objective: To study and compare the immunologic function and antioxidative effect of Tongcao(Tongtuou) Xiao Tongcao(Ximashanjingjehua, Xinanxiuqiu, Ditanghua) polysaccharides. Method: Mice were abdominally administrated with four kinds of polysaccharides at dosages of 80mg/kg and 40mg/kg for 7 apprx 10 days. Result: Four kinds of polysaccharides could increase the serum-lysozyme activity, phagocytic function of MPS and the serum hemolysin-antibody level in mice, inhibit the delayed hypersensitivity induced by DNCB in mice and raise the serum-catalase activity in mice. Conclusion: Four kinds of Tongcao or Xiao-Tongcao polysaccharides have immunoregulative function and antioxidative effect. The results could enrich the contents of "A Study on Species-Sorting and Quality of Tongcao-Xiao-Tongcao Crude Drugs".

4/AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011658146 BIOSIS NO.: 199800452393
Indirect fluorescent antibody test for the diagnosis and therapeutic evaluation of trichinosis
AUTHOR: Cui Jing; Wang Zhongquan (Reprint); Wu Feng; Jin Xuexiang (Reprint); Zhang Pengyuan; Yang Ruiqin; Liu Jun
AUTHOR ADDRESS: Dep. Parasitol., Henan Med. Univ., Zhengzhou 450052, China**China
JOURNAL: Chinese Medical Journal (English Edition) 111 (5): p449 May, 1998 1998
MEDIUM: print
ISSN: 0366-6999
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English

4/AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011389070 BIOSIS NO.: 199800183317
Inhibition of HIV-1 gp120-induced apoptosis in neuroblastoma SK-N-SH cells by an antisense oligodeoxynucleotide against p53
AUTHOR: Yeung Michael C; Geertsma Francesca; Liu Jun; Lau Allan S (Reprint)
AUTHOR ADDRESS: Room 6E6, San Francisco Gen. Hosp., 1001 Potrero Ave., San Francisco, CA 94110, USA**USA
JOURNAL: AIDS (London) 12 (4): p349-354 March 5, 1998 1998
MEDIUM: print
ISSN: 0269-9370
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objectives: This study examines the cytotoxicity potential and the mechanism of toxicity of the HIV-1 gp120 on human neuroblastoma cells. Design: Previous data from our group have suggested that the HIV-1 envelope protein gp120 promotes the secretion of tumor necrosis factor-alpha and other factors by astrocytes and microglial cells present in primary human brain cell cultures, thereby contributing to the injury of neurons in these cultures. This study investigates the cytotoxicity potential and the mechanism of toxicity of gp120 on human neuroblastoma cells. Methods: SK-N-SH cells were treated with HIV-1 gp120, and was followed by in situ DNA fragmentation staining and small molecular weight DNA extraction studies to ascertain the induction of apoptosis by gp120 in these cells. To evaluate a potential role of the growth suppressor gene p53, gp120-treated SK-N-SH cells were subjected to reverse transcription polymerase chain reaction (RT-PCR) and Western blot analyses for the induction of p53. An antisense oligodeoxynucleotide against p53 was used to investigate the role of p53 in the gp120-induced apoptosis in these cells. Results: Data from T7 DNA polymerase staining and small molecular weight DNA extraction studies demonstrated that gp120-induced DNA breakage in SK-N-SH cells with fragmentation patterns characteristic of apoptosis. RT-PCR and Western blot analyses revealed that the gp120-mediated induction of apoptosis was dependent on a gp120-induced and gp120-sustained upregulation of p53. The induction of p53 by gp120 was specific, since an antibody against gp120 prevented both the induction of p53 and subsequent apoptosis in SK-N-SH cells. The critical role of p53 was further illustrated by the effectiveness of a p53 antisense oligodeoxynucleotide to inhibit the gp120-induced apoptosis. As a control, the apoptosis-inducing potential of gp120 on SK-N-SH cells was not seen in the HIV-1 Gag proteins even when used at up to 5 nM. Conclusions: These results established that HIV-1 gp120 is potentially cytotoxic to human neuronal cells through the induction of p53, which may eventually lead to induction of apoptosis.

4/AB/10 (Item 10 from file: 5)

0011180770 BIOSIS NO.: 199799814830
Interaction of human IgE with soluble forms of IgE high affinity receptors
AUTHOR: Liu Jun (Reprint); Ruppel Jane; Shire Steven J
AUTHOR ADDRESS: Dep. Pharm. Res. Dev., Genentech Inc., S. San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 14 (10): p1388-1393 1997 1997
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. Interaction of human IgE with its high affinity receptor (Fc-epsilon-RI) on mast cells and basophils is art important step for initiating IgE mediated immune responses. To characterize the IgE and Fc-epsilon-RI interaction, we investigated this interaction in terms of stoichiometry and binding affinity in solution. The binding of IgE and IgE Fc-epsilon-RI alpha chain, the extracellular portion of IgE high affinity receptor (sFc-epsilon-RI-alpha) was compared with the binding of IgE and IgE immunoadhesin (Fc-epsilon-RI-alpha-IgG). Methods. The interaction was characterized by analytical ultracentrifugation, size exclusion chromatography, light scattering and ELISA. Results. We show that the sFc-epsilon-RI-alpha is only able to bind to one IgE, while the immunoadhesin can bind to two IgE. The interaction between IgE and Fc-epsilon-RI is very strong. Both forms of soluble receptors have similar intrinsic binding affinity with IgE. Conclusions. Both soluble receptors (Fc-epsilon-RI-alpha-IgG and sFc-epsilon-RI-alpha) can block the binding of IgE to its high affinity receptors on cell surface. The Fc-epsilon-RI-alpha-IgG is a better IgE binding protein than sFc-epsilon-R-alpha at physio logical relevant conditions. A humanized anti-IgE monoclonal antibody, rhuMAb E25 that also can block the binding of IgE to its high affinity receptors appears to bind to IgE at slightly different regions or in a different manner as the soluble forms of IgE receptors.

4/AB/11 (Item 11 from file: 5)

0011071236 BIOSIS NO.: 199799705296

Hypoosmotic exposure of canine pancreatic digest as a means to purify islet tissue

AUTHOR: Lakey Jonathan R T (Reprint); Zieger Michael A J; Woods Erik J; Liu Jun; Critser John K
AUTHOR ADDRESS: Cryobiol. Res. Inst., Methodist Hosp. Indiana Inc., Indianapolis, IN 46206, USA**USA

JOURNAL: Cell Transplantation 6 (4): p423-428 1997 1997
ISSN: 0963-6897
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The development of more effective means to separate pancreatic islets from the unwanted exocrine tissue would greatly advance the field of clinical islet allotransplantation in the treatment of insulin-dependent diabetes mellitus. Recent experiments with hamster islets have demonstrated a selective destruction of dissociated single exocrine cells when exposed to hypotonic conditions. It was the aim of this study to extend these observations to the canine model with collagenase dissociated pancreatic tissue and to evaluate the treatment's effect on islet function. Pancreases from rive mongrel dogs were digested using an automated protocol of intraductal delivery of collagenase, and gentle dissociation. Duplicate samples or pancreatic digest were removed for insulin and amylase determination prior to and immediately following exposure to 50 mOsm/kg salt solution for a period or 30, 60, or 300 s before returning the digest to isoosmotic conditions. The remaining digest was cultured for a period of 48 h at 37 degree C before the tissue was recombined, washed, and a third sample removed for insulin and amylase. In vitro viability was then assessed using a static incubation assay with insulin content measured using a double-antibody

radioimmunoassay, and amylase was determined using a colorimetric assay system. No difference in the insulin or amylase levels between the experimental groups was observed immediately following the hypotonic exposure; however, a significant decrease in the amylase content was observed following the 48-h culture period in digest that had been hypoosmotically exposed for 60 or 300 s compared with the pretreatment group (2.83 +- 0.41 IU amylase/mg pancreas vs. 1.29 +- 0.21 and 0.83 +- 0.12, mean +- SEM, p lt 0.05). Insulin content was also significantly reduced in the 300-s exposure group compared with nontreated controls (3.2 +- 0.6 mU insulin/mg pancreas vs. 2.0 +- 0.2). The insulin/ amylase ratio (I/A), a measure of islet and exocrine content, was 1.1 +- 0.13 following pancreas dissociation and 1.34 +- 0.21 for control tissue cultured for 48 h. The I/A ratio increased following hypoosmotic exposure to 1.50 +- 0.31 for tissue exposed for 30 s, 1.77 +- 0.19 for 60-s exposure, and 2.54 +- 0.13 for tissue exposed for 300 s (p lt 0.05, vs. pretreatment group). In vitro insulin secretion was equivalent with the exception of the tissue exposed for 300 s, which had an increased basal level of insulin resulting in a significantly decreased stimulation index (3.8 +- 0.5 vs. 8.1 +- 1.2 for the purified islet control group, p lt 0.05). These results suggest that a brief hypotonic exposure to pancreatic digest can alter the insulin/amylase ratio; however, there is a functional impairment on subsequent islet function after a period of in vitro tissue culture.

4/AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010671993 BIOSIS NO.: 199799306053
Fast determination of the relative binding activity of rhuMAb E25 with optical biosensor
AUTHOR: Liu Jun; Gray Rebecca; Shire Steve J
AUTHOR ADDRESS: Pharm. R and D, Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.): pS102 1996 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996; 19961027
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010107307 BIOSIS NO.: 199698575140
A novel solution based receptor inhibition assay to evaluate the interaction of anti-IgE monoclonal antibody and its Fab mutant to IgE
AUTHOR: Liu Jun; Shire Steven J
AUTHOR ADDRESS: Pharm R D, Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 12 (9 SUPPL.): pS96 1995 1995
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Miami Beach, Florida, USA November 5-9, 1995; 19951105
ISSN: 0724-8741

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

4/AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010048867 BIOSIS NO.: 199598516700
Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE
AUTHOR: Liu Jun; Lester Philip; Builder Stuart; Shire Steven J (Reprint)
AUTHOR ADDRESS: Pharm. Res. Dev., Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Biochemistry 34 (33): p10474-10482 1995 1995
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The interaction of human IgE with high-affinity IgE F-c receptors on cells of the immune system plays an essential role in the type I hypersensitivity reaction. A proposed therapy is to use an anti-IgE monoclonal antibody to block the binding of IgE to its high-affinity receptor on mast cells and basophils, thus preventing subsequent release of the inflammatory agents after exposure to allergen. We report here the solution characteristics of immune complexes formed by a humanized anti-IgE monoclonal antibody (rhuMAb E25) and IgE using sedimentation analysis and size exclusion chromatography. We demonstrate that the rhuMAb E25 is able to form a variety of complexes with IgE at different molar ratios. The largest complex was identified by sedimentation equilibrium analysis as a heterohexamer with very high stability. The intermediate complex formed when one of the interacting components is in large molar excess appears to have a trimeric structure. The high-affinity interaction of rhuMAb E25 and IgE has also been confirmed. Furthermore, by using hydrodynamic modeling, we show that the largest complex may be represented by a cyclic structure.

4/AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009551954 BIOSIS NO.: 199598019787
Thermodynamic analysis of immune complex formation by humanized anti-IgE antibody and IgE
AUTHOR: Liu Jun; Lester Philip; Builder Stuart; Shire Steven
AUTHOR ADDRESS: Pharm R and D Process Sci., Genenetech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 11 (10 SUPPL.): pS74 1994 1994
CONFERENCE/MEETING: Ninth Annual Meeting of the American Association of Pharmaceutical Scientists San Diego, California, USA November 6-10, 1994; 19941106
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

4/AB/16 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

17276335 PMID: 15504729
Loss of caveolin-1 polarity impedes endothelial cell polarization and directional movement.
Beardsley Andrew; Fang Kai; Mertz Heather; Castranova Vince; Friend Sherri; Liu Jun
Mary Babb Randolph Cancer Center and Departments of Physiology and Pharmacology, and Obstetrics and Gynecology, West Virginia University, Morgantown, West Virginia 26506, USA.
Journal of biological chemistry (United States) Feb 4 2005, 280 (5) p3541-7, ISSN 0021-9258 Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The ability of a cell to move requires the asymmetrical organization of cellular activities. To investigate polarized cellular activity in moving endothelial cells, human endothelial cells were incubated in a Dunn chamber to allow migration toward vascular endothelial growth factor. Immunofluorescent staining with a specific antibody against caveolin-1 revealed that caveolin-1 was concentrated at the rear of moving cells. Similarly, monolayer scraping to induce random cell walk resulted in relocation of caveolin-1 to the cell rear. These results suggest that posterior polarization of caveolin-1 is a common feature both for chemotaxis and chemokinesis. Dual immunofluorescent labeling showed that, during cell spreading, caveolin-1 was compacted in the cell center and excluded from nascent focal contacts along the circular lamellipodium, as revealed by integrin beta1 and FAK staining. When cells were migrating, integrin beta1 and FAK appeared at polarized lamellipodia, whereas caveolin-1 was found at the posterior of moving cells. Notably, wherever caveolin-1 was polarized, there was a conspicuous absence of lamellipod protrusion. Transmission electron microscopy showed that caveolae, similar to their marker caveolin-1, were located at the cell center during cell spreading or at the cell rear during cell migration. In contrast to its unphosphorylated form, tyrosine-phosphorylated caveolin-1, upon fibronectin stimulation, was associated with the focal complex molecule phosphopaxillin along the lamellipodia of moving cells. Thus, unphosphorylated and phosphorylated caveolin-1 were located at opposite poles during cell migration. Importantly, loss of caveolin-1 polarity by targeted down-regulation of the protein prevented cell polarization and directional movement. Our present results suggest a potential role of caveolin polarity in lamellipod extension and cell migration.

4/AB/17 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15203683 PMID: 14969833
Lamivudine prophylaxis of liver allograft HBV reinfection in HBV related cirrhotic patients after liver transplantation.
Lu Shi-Chun; Yan Lu-Nan; Li Bo; Wen Tian-Fu; Zhao Ji-Chun; Cheng Nan-Sheng; Liu Chong; Liu Jun; Wang Xiao-Bo; Li Xiao-Dong; Qin Shan; Zhao Lian-Shan; Lei Bin-Jun; Zhang Xiu-Hui
Department of General Surgery, West China Hospital, Sichuan University, Chengdu 610041, China. lsc620213@medmail.com.cn

Hepatobiliary & pancreatic diseases international - HBPD INT (China)
Feb 2004, 3 (1) p26-32, ISSN 1499-3872 Journal Code: 101151457
Publishing Model Print
Document type: Clinical Trial; Controlled Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

BACKGROUND: Liver allograft hepatitis B virus (HBV) reinfection and hepatitis B (HB) recurrence jeopardize the long-term survival of recipient and liver allograft. Lamivudine has been referred as a novel antiviral agent against HBV in HBV cirrhotic patients even in liver transplantation setting. We assessed the prophylatic effect of lamivudine on liver allograft HBV reinfection and clarified the dynamic changes of HBV markers in HBV related decompensated liver cirrhosis after liver transplantation. METHODS: Twenty-five recipients were divided into three groups: HBV active replication group (15 recipients), HBV inactive replication group (7), and control group (3). 100 mg/d lamivudine was administered preoperatively except in the control group. The HBV markers of serial sera and liver biopsy samples of the 25 recipients were evaluated regularly with enzyme-linked radioimmunoassay, HBV DNA fluorescent quantitative assay, immunohistochemical staining, labelled streptavidin biotin (LSAB) and digoxin labelled HBV DNA hybridization in situ. The dynamic alternation of HBV markers under lamivudine prophylaxis was observed. RESULTS: In the HBV active replication group who had received lamivudine 2 weeks before liver transplantation, serum HBV DNA positive converted to negative by 80%. HBsAg of all recipients disappeared after liver transplantation, but corresponding antibodies of HBV appeared within one week after the operation. HBsAb 9/15, HBcAb 13/15 and HBeAb 11/15 appeared and subsided gradually within 24 weeks. HBV DNA in sera was kept negative; HBsAg, HBcAg and HBV DNA hybridization in situ of liver biopsy samples remained negative after use of lamivudine. Ten of the 15 recipients showed clearance of HBV, and per se HBV markers were undetectable both in serum and liver biopsy samples between 12 to 44 weeks (24 weeks on average). The 1-, 2-year survival rates were 83% in this group. Two of the 15 recipients developed HBV allograft reinfection or recurrence of hepatitis 2 years after lamivudine monoprophylaxis (2/15, 13.3%). In the HBV inactive replication group, the outcome was similar to that of the HBV active group. The HBV antibody frequency was HBsAb 4/7, HBcAb 6/7, and HBeAb 2/7. Three of 7 recipients showed HBV clearance both in sera and liver biopsy samples, whereas in the control group all 3 recipients developed HBV allograft reinfection and recurrent hepatitis 8, 10, 12 months postoperatively; one of them died of fibrosing cholestatic hepatitis, and the remaining 2 recovered after additional lamivudine therapy. The overall allograft reinfection rate was 9.1% (2/22) and the overall 1-, 2-year survival rates were 87% in the lamivudine prophylaxis group. CONCLUSIONS: Lamivudine prophylaxis can prevent effectively liver allograft from HBV reinfection in patients with HBV-related decompensated liver cirrhosis even in HBV active replication recipient after liver transplantation. Its long-term outcome remains to be studied.

4/AB/18 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14873409 PMID: 12854151
Inhibition of HBV targeted ribonuclease enhanced by introduction of linker.
Gong Wei-Dong; Liu Jun; Ding Jin; Zhao Ya; Li Ying-Hui; Xue Cai-Fang
Department of Pathogenic Organisms, Fourth Military Medical University,

Xi'an 710033, Shaanxi Province, China.
World journal of gastroenterology - WJG (China) Jul 2003, 9 (7) p1504-7, ISSN 1007-9327 Journal Code: 100883448
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

AIM: To construct human eosinophil-derived neurotoxin(hEDN) and HBV core protein (HBVc) eukaryotic fusion expression vector with a linker (Gly(4)Ser) (3) between them to optimize the molecule folding, which will be used to inhibit HBV replication in vitro. METHODS: Previously constructed pcDNA3.1(-)/TR was used as a template. Linker sequence was synthesized and annealed to form dslinker, and cloned into pcDNA3.1(-)/TR to produce plasmid pcDNA3.1(-)/HBc-linker. Then the hEDN fragment was PCR amplified and inserted into pcDNA3.1(-)/HBc-linker to form pcDNA3.1(-)/TNL in which the effector molecule and the target molecule were separated by a linker sequence. pcDNA3.1(-)/TNL expression was identified by indirect immunofluorescence staining. Radioimmunoassay was used to analyse anti-HBV activity of pcDNA3.1(-)/TNL. Meanwhile, metabolism of cells was evaluated by MTT colorimetry. RESULTS: hEDN and HBVc eukaryotic fusion expression vector with a linker (Gly(4)Ser)(3) between them was successfully constructed. pcDNA3.1(-)/TNL was expressed in HepG2.2.15 cells efficiently. A significant decrease of HBsAg concentration from pcDNA3.1(-)/TNL transfectant was observed compared to pcDNA3.1(-)/TR (P=0.036, P<0.05). MTT assay suggested that there were no significant differences between groups (P=0.08, P>0.05). CONCLUSION: Linker introduction enhances the inhibitory effect of HBV targeted ribonuclease significantly.

4/AB/19 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14437692 PMID: 12376270
[Experimental study of monoclonal antibody to intercellular adhesion molecule-1 for incipient acute tubular necrosis]
Liu Jun; Wang Li; Wang Xiao-Ning
Department of Nephrology, Nanfang Hospital,First Military Medical University, Guangzhou 510515, China.
Di yi jun yi da xue xue bao = Academic journal of the First Medical College of PLA (China) Aug 2002, 22 (8) p748-50, ISSN 1000-2588 Journal Code: 9426110
Publishing Model Print
Document type: Journal Article ; English Abstract
Languages: CHINESE
Main Citation Owner: NLM
Record type: MEDLINE; Completed

OBJECTIVE: To explore the role of leukocyte adhesion in the pathophysiology of glycerol-induced acute renal tubular necrosis (ATN). METHODS: Rat models of ATN were established by intramuscular injection of glycerol in 24 Wistar rats, which were divided randomly into 3 groups of equal number according to the agents coinjected with glycerol for the prevention of ATN, with another 8 rats serving as normal control. One of the 3 groups received a monoclonal antibody (mAb) against intercellualr adhesion molecule-1 (anti-ICAM-1) and another received CD3 mAb, leaving one group untreated. Both functional impairment and histological changes in the rats were observed. RESULTS: Plasma creatinine measured 24 h after the injection of glycerol was 412.31+/-94.42 micromol/L in rats treated with anti-ICAM-1, significantly lower than that in CD3 mAb-treated rats (990.21

+/-171.25 micromol/L, P<0.05). Moderate to severe necrosis in the outer renal medulla with frequent mitoses was present in rats with ATN receiving CD3 mAB or nothing, but only mild necrosis with few mitoses occurred in merely 2 of those rats with anti-ICAM-1 treatment. CONCLUSION: Leukocytes and adhesion molecules play critical roles in the pathophysiology of glycerol-induced ATN, and anti-ICAM-1 which blocks the adhesion of the leukocytes may alleviate the pathological changes in the kidney.
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Set	Items	Description
S1	621	E3-E12
S2	509	RD S1 (unique items)
S3	19	S2 AND ANTIBODY
S4	19	RD S3 (unique items)

?

Steve Shire

TYPE S5/MEDIUM,AB/1-46

5/AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015011012 BIOSIS NO.: 200400381801
Commercial manufacturing scale formulation and analytical characterization of therapeutic recombinant antibodies
AUTHOR: Harris Reed J (Reprint); Shire Steven J; Winter Charles
AUTHOR ADDRESS: Recovery Sci, Genentech Inc, 62,1 DNA Way, S San Francisco, CA, 94080, USA**USA
AUTHOR E-MAIL ADDRESS: reed@gene.com
JOURNAL: Drug Development Research 61 (3): p137-154 March 2004 2004
MEDIUM: print
ISSN: 0272-4391 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Stable therapeutic antibody dosage forms present production technology challenges, particularly when high-concentration formulations are needed to meet the elevated dose requirements that are generally required for successful antibody therapy. Solid dosage forms, such as lyophilized powders, are generally more stable than liquid formulations. High-concentration drug products can be achieved by reconstitution of the lyophilisate in a smaller volume than its initial (pre-lyophilization) volume, but requires a significant vial overfill. High-concentration liquid formulations are becoming feasible as new techniques and technologies become available. Analytical methods to detect subtle molecular variations have been developed to demonstrate manufacturing consistency. Some molecular heterogeneity is contributed by conserved sites, such as Asn297 glycosylation and the loss of heavy chain C-terminal Lys residues. Characteristics that affect potency, stability, or immunogenicity must be elucidated for each therapeutic antibody. Copyright 2004 Wiley-Liss, Inc.

5/AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014946281 BIOSIS NO.: 200400317038
Challenges in the development of high protein concentration formulations
AUTHOR: Shire Steven J (Reprint); Shahrokh Zahra; Liu Jun
AUTHOR ADDRESS: Dept Pharmaceut R and D, Genentech Inc, S San Francisco, CA, 94080, USA**USA
AUTHOR E-MAIL ADDRESS: steveshire@gene.com
JOURNAL: Journal of Pharmaceutical Sciences 93 (6): p1390-1402 June 2004 2004
MEDIUM: print
ISSN: 0022-3549
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Development of formulations for protein drugs requiring high dosing (in the order of mg/kg) may become challenging for solubility limited proteins and for the subcutaneous (SC) route with <1.5 mL allowable administration volume that requires >100 mg/mL protein

concentrations. Development of high protein concentration formulations also results in several manufacturing, stability, analytical, and delivery challenges. The high concentrations achieved by small scale approaches used in preformulation studies would have to be confirmed with manufacturing scale processes and with representative materials because of the lability of protein conformation and the propensity to interact with surfaces and solutes which render protein solubilities that are dependent on the process of concentrating. The concentration dependent degradation route of aggregation is the greatest challenge to developing protein formulations at these higher concentrations. In addition to the potential for nonnative protein aggregation and particulate formation, reversible self-association may occur, which contributes to properties such as viscosity that complicates delivery by injection. Higher viscosity also complicates manufacturing of high protein concentrations by filtration approaches. Chromatographic and electrophoretic assays may not accurately determine the noncovalent higher molecular weight forms because of the dilutions that are usually encountered with these techniques. Hence, techniques must be used that allow for direct measurement in the formulation without substantial dilution of the protein. These challenges are summarized in this review. Copyright 2004 Wiley-Liss, Inc. and the American Pharmacists Association.

5/AB/3 (Item 3 from file: 5)

0014759935 BIOSIS NO.: 200400130692

Protein formulation

AUTHOR: Andya James (Reprint); Cleland Jeffrey L; Hsu Chung C; Lam Xanthe M ; Overcashier David E; Shire Steven J; Yang Janet Yu-Feng; Wu Sylvia Sau-Yan

JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1279 (1): Feb. 3, 2004 2004
MEDIUM: e-file
PATENT NUMBER: US 6685940 PATENT DATE GRANTED: February 03, 2004 20040203
PATENT CLASSIFICATION: 424-1331 PATENT ASSIGNEE: Genentech, Inc.
PATENT COUNTRY: USA
ISSN: 0098-1133 _(ISSN print)
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration. For example, anti-IgE and anti-HER2 antibody formulations have been prepared by lyophilizing these antibodies in the presence of a lyoprotectant. The lyophilized mixture thus formed is reconstituted to a high protein concentration without apparent loss of stability of the protein.

5/AB/4 (Item 4 from file: 5)

0014411167 BIOSIS NO.: 200300369886

Correlation of physical and chemical stability of rhDNase with melting temperature.

AUTHOR: Cromwell Mary E M (Reprint); Patapoff Thomas (Reprint); Shire Steven J (Reprint)
AUTHOR ADDRESS: Pharmaceutical R and D, Genentech, Inc, 1 DNA Way, MS96A, South San Francisco, CA, 94080-4918, USA**USA
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JOURNAL: Abstracts of Papers American Chemical Society 225 (1-2): pBIOT 8 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 225th American Chemical Society (ACS) National Meeting New Orleans, LA, USA March 23-27, 2003; 20030323
SPONSOR: American Chemical Society
ISSN: 0065-7727 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013951370 BIOSIS NO.: 200200544881
Purified forms of DNase
AUTHOR: Frenz John (Reprint); Shire Steven J; Sliwkowski Mary B
AUTHOR ADDRESS: Millbrae, CA, USA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1261 (4): Aug. 27, 2002 2002
MEDIUM: e-file
PATENT NUMBER: US 6440412 PATENT DATE GRANTED: August 27, 2002 20020827
PATENT CLASSIFICATION: 424-9461 PATENT ASSIGNEE: Genentech, Inc.
PATENT COUNTRY: USA
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention provides the identification and characterization of two components of a recombinant preparation of DNase. These components are the purified deamidated and non-deamidated human DNases. Taught herein are the separation of these components and the use of the non-deamidated species as a pharmaceutical per se, and in particular in compositions wherein the species is disclosed within a plastic vial, for use in administering to patients suffering from pulmonary distress.

5/AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013741088 BIOSIS NO.: 200200334599
Minimizing thermally induced aggregation of DNase in solution with calcium
AUTHOR: Chan Hak-Kim (Reprint); Gonda Igor; Shire Steven J; Weck Suzanne Sin-Mui Lo
AUTHOR ADDRESS: North Sydney, Australia**Australia
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1258 (1): May 7, 2002 2002
MEDIUM: e-file
PATENT NUMBER: US 6383788 PATENT DATE GRANTED: May 07, 2002 20020507
PATENT CLASSIFICATION: 435-188 PATENT ASSIGNEE: Genentech, Inc.

PATENT COUNTRY: USA
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention relates to the use of calcium ion and/or sugars to minimize thermal aggregation of DNase and to the use of calcium ion to stabilize liquid solutions of DNase, the solutions having a pH of less than neutral. DNase is the active pharmaceutical principle and the solutions may contain other pharmaceutically acceptable excipients making them suitable for pharmaceutical administration. In the first instance, calcium ion/sugar minimizes the effects of thermal aggregation in the solution. In the second aspect, calcium ion stabilizes the lower pH solutions from protein precipitation.

5/AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013267632 BIOSIS NO.: 200100439471
Protein formulation
AUTHOR: Andya James (Reprint); Cleland Jeffrey L; Hsu Chung C; Lam Xanthe M ; Overcashier David E; Shire Steven J; Yang Janet Yu-Feng; Wu Sylvia Sau-Yan
AUTHOR ADDRESS: Millbrae, CA, USA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1248 (5): July 31, 2001 2001
MEDIUM: e-file
PATENT NUMBER: US 6267958 PATENT DATE GRANTED: July 31, 2001 20010731
PATENT CLASSIFICATION: 424-1301 PATENT ASSIGNEE: Genentech, Inc.
PATENT COUNTRY: USA
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration. For example, anti-IgE and anti-HER2 antibody formulations have been prepared by lyophilizing these antibodies in the presence of a lyoprotectant. The lyophilized mixture thus formed is reconstituted to a high protein concentration without apparent loss of stability of the protein.

5/AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012991096 BIOSIS NO.: 200100162935
Identification of multiple sources of charge heterogeneity in a recombinant antibody
AUTHOR: Harris Reed J (Reprint); Kabakoff Bruce; Macchi Frank D; Shen Felicity J; Kwong May; Andya James D; Shire Steven J; Bjork Nancy; Totpal Klara; Chen Anthony B
AUTHOR ADDRESS: Analytical Chemistry Department, Genentech Inc., 1 DNA Way, South San Francisco, CA, 94080, USA**USA

JOURNAL: Journal of Chromatography B 752 (2): p233-245 10 March, 2001 2001
MEDIUM: print
ISSN: 0378-4347
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Seven forms of a therapeutic recombinant antibody that binds to the her2/neu gene product were resolved by cation-exchange chromatography. Structural differences were assigned by peptide mapping and HIC after papain digestion. Deamidation of light chain asparagine 30 to aspartate in one or both light chains is responsible for two acidic forms. A low potency form is due to isomerization of heavy chain aspartate 102; the Asp102 succinimide is also present in a basic peak fraction. Forms with both Asn30 deamidation and Asp102 isomerization modifications were isolated. Deamidation of heavy chain Asn55 to isoaspartate was also detected. Isoelectric focusing in a polyacrylamide gel was used to verify the assignments. All modifications were found in complementarity determining regions.

5/AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012626453 BIOSIS NO.: 200000344766
Evidence for the involvement of Histidine A(12) in the aggregation and precipitation of human relaxin induced by metal-catalyzed oxidation
AUTHOR: Khossravi Mehrnaz; Shire Steven J; Borchardt Ronald T (Reprint)
AUTHOR ADDRESS: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS, 66047, USA**USA
JOURNAL: Biochemistry 39 (19): p5876-5885 May 16, 2000 2000
MEDIUM: print
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The metal-catalyzed oxidation (ascorbate/cupric chloride/oxygen) of recombinant human relaxin (rhRlx, type II) was shown by Li et al. (Li, S., Nguyen, T. H., Schoneich, C., and Borchardt, R. T. (1995) Biochemistry 34, 5762-5772) to result in the chemical modification of His A(12), Met B(4), and Met B(25). Considering the fact that His A(12) exists in an extended loop that joins two alpha-helices in this protein, we hypothesized that oxidation of this specific amino acid leads to alterations in the secondary and tertiary structures of the protein, resulting in the pH-dependent aggregation/precipitation phenomena observed in our earlier studies (i.e., at pH >6.0 most of the degradants of rhRlx are insoluble). Evidence obtained in the current study that supports this hypothesis includes the following: (i) oxidation of rhRlx with hydrogen peroxide (H2O2), which leads only to modification of Met B(4) and Met B(25), does not result in the pH-dependent aggregation/precipitation of the protein; and (ii) metal-catalyzed oxidation of porcine relaxin (pRlx), which does not contain His at position A(12), leads to chemical degradation of the protein (e.g., Met A(2) is oxidized) but produces only slight pH-dependent aggregation/precipitation of the protein. In addition, experimental evidence is provided to show that the physical instability of rhRlx observed at pH >6.0 does not appear to be related to the pH-dependent solubility of a common protein degradant. Instead, it appears that

several oxidation products of His A(12) are produced in a pH-dependent manner and that these oxidation products produce different effects on the physical stability of the protein. Evidence in support of this conclusion includes the observation that the soluble degradants of rhRlx showed reduced levels of His, reduced levels of the T2-T7 tryptic fragment that contained His A(12), and the presence of 2-oxo-His. Similarly, the precipitated degradants of rhRlx showed reduced levels of His but no 2-oxo-His. In addition, the soluble degradants, which contain 2-oxo-His, appear to exist as monomers having an average molecular weight similar to that of rhRlx. These results suggest that the metal-catalyzed oxidation of His A(12) leads to other, as yet unidentified oxidation products of His A(12) that affect the secondary/tertiary structure of the protein more significantly than does 2-oxo-His and ultimately lead to the physical instability of the protein observed at higher pH values.

5/AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012261797 BIOSIS NO.: 199900521457
Human relaxin formulation
AUTHOR: Cipolla David C (Reprint); Nguyen Tue H; Shire Steven J
AUTHOR ADDRESS: Danville, CA, USA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1225 (5): Aug. 31, 1999 1999
MEDIUM: print
PATENT NUMBER: US 5945402 PATENT DATE GRANTED: Aug. 31, 1999 19990831
PATENT CLASSIFICATION: 514-21 PATENT ASSIGNEE: Genetech, Inc.
PATENT COUNTRY: USA
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Citation
LANGUAGE: English

5/AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012179486 BIOSIS NO.: 199900439146
Challenges and issues in the development of formulations of protein pharmaceuticals
BOOK TITLE: Biopharmaceutical drug design and development
AUTHOR: Shire Steven J (Reprint)
BOOK AUTHOR/EDITOR: Wu-Pong S (Editor); Rojanasakul Y (Editor)
AUTHOR ADDRESS: Genentech, South San Francisco, CA, USA**USA
p205-238 1999
MEDIUM: print
BOOK PUBLISHER: Humana Press Inc. {a}, Suite 808, 999 Riverview Drive, Totowa, New Jersey 07512, USA
ISBN: 0-89603-691-X
DOCUMENT TYPE: Book; Book Chapter
RECORD TYPE: Citation
LANGUAGE: English

5/AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012059636 BIOSIS NO.: 199900319296

Investigation of protein-surfactant interactions by analytical ultracentrifugation and electron paramagnetic resonance: The use of recombinant human tissue factor as an example

AUTHOR: Jones LaToya S; Cipolla David; Liu Jun; Shire Steven J (Reprint); Randolph Theodore W

AUTHOR ADDRESS: Dept. of Pharmaceutical Research and Development, MS 19, Genentech, Inc., 1 DNA Way, S. San Francisco, CA, 94080, USA**USA

JOURNAL: Pharmaceutical Research (New York) 16 (6): p808-812 June, 1999 1999

MEDIUM: print

ISSN: 0724-8741

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Purpose. The purpose of this work is to utilize electron paramagnetic resonance (EPR) spectroscopy in conjunction with analytical ultracentrifugation (AUC) to investigate the binding of surfactants to proteins with a transmembrane domain. As an example these methods have been used to study the interaction of a nonionic surfactant, C12E8, to recombinant human tissue factor (rhTF) in liquid formulations. The complementary nature of the two techniques aids in data interpretation when there is ambiguity using a single technique. In addition to binding stoichiometries, the possibility of identifying the interacting domains by using two forms of rhTF is explored. Methods. Two recombinant, truncated forms of human tissue factor were formulated in the absence of phospholipids. Neither of the recombinant proteins, produced in E. coli, contains the cytoplasmic domain. Recombinant human tissue factor 243 (rhTF 243) consists of 243 amino acids and includes the transmembrane sequences. Recombinant human tissue factor 220 (rhTF 220), however, contains only the first 221 amino acids of the human tissue factor, lacking those of the transmembrane region. EPR and AUC were used to investigate the interactions between these two forms of rhTF and polyoxyethylene 8 lauryl ether, C12E8. Results. Binding of C12E8 to rhTF 243 is detected by both EPR spectroscopy and AUC. Although a unique binding stoichiometry was not determined, EPR spectroscopy greatly narrowed the range of possible solutions suggested by the AUC data. Neither technique revealed an interaction between rhTF 220 and C12E8. Conclusions. The complementary nature of EPR spectroscopy and AUC make the combination of the two techniques useful in data interpretation when studying the interactions between rhTF and C12E8. By utilizing these techniques in this study, the binding stoichiometry of rhTF 243 to C12E8 ranges from 1.2:1 to 1.3:0.6 based on an aggregation number of 120. This binding is consistent with previously reported activity data that showed an increase in clotting rate when rhTF 243 is in the presence of C12E8 micelles. From the rhTF 220 data, it can further be concluded that the transmembrane domain of rhTF is necessary for interactions with C12E8.

5/AB/13 (Item 13 from file: 5)

0011976582 BIOSIS NO.: 199900236242

Influence of calcium ions on the structure and stability of recombinant human deoxyribonuclease I in the aqueous and lyophilized states

AUTHOR: Chen Bei; Costantino Henry R; Liu Jun; Hsu Chung C; Shire Steven J (Reprint)

AUTHOR ADDRESS: Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080, USA**USA
JOURNAL: Journal of Pharmaceutical Sciences 88 (4): p477-482 April, 1999 1999
MEDIUM: print
ISSN: 0022-3549
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of calcium ions on the structure and stability of recombinant human DNase I (rhDNase) in the aqueous and solid (lyophilized) states was investigated. Fourier transform infrared (FTIR) spectroscopy was used to examine the overall secondary structure, while chemical stability was monitored in terms of deamidation and soluble aggregate formation at 40 degreeC. The exogenous calcium was removed by EGTA. This process can remove all but approximately one calcium ion per protein molecule. Analysis of the FTIR spectra in the amide III region in either the aqueous or lyophilized state demonstrated that removal of exogenous Ca2+ by EGTA-treatment had little effect on the secondary structure (and lyophilization-induced rearrangement thereof). For the aqueous solution, circular dichroism was used as an independent technique and confirmed that there was no large overall change in the secondary or tertiary structure upon the removal of calcium. The primary degradation route for the aqueous protein was deamidation. For the EGTA-treated protein, there was also severe covalent aggregation, e.g., formation of intermolecular disulfides facilitated by the cleavage of Cys173-Cys209. The aggregates exhibited a markedly different secondary structure compared to the native protein. For instance, the beta-sheet band observed at ca. 1620 cm-1 wavenumber in the amide I second derivative spectra was increased. Enzymatic activity was completely lost upon aggregation, consistent with the cleavage of the aforementioned native disulfide. For the protein lyophilized in the presence of Ca2+, there was no increase in deamidated species during solid-state storage; however, some aggregation was observed. For the lyophilized EGTA-treated protein, aggregation was even more pronounced, and there was some loss in enzymatic activity upon reconstitution. Thus, the removal of calcium ions by EGTA-treatment decreased the stability of rhDNase in both the aqueous and solid states even though no large overall calcium-induced structural changes could be observed by the techniques used in this study.

5/AB/14 (Item 14 from file: 5)

0011949786 BIOSIS NO.: 199900209446
The effect of formulation excipients on protein stability and aerosol performance of spray-dried powders of a recombinant humanized anti-igE monoclonal antibody
AUTHOR: Andya James D (Reprint); Maa Yuh-Fun; Costantino Henry R; Nguyen Phuong-Anh; Dasovich Nancy; Sweeney Theresa D; Hsu Chung C; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 16 (3): p350-358 March, 1999 1999
MEDIUM: print
ISSN: 0724-8741
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. To study the effect of trehalose, lactose, and mannitol on the biochemical stability and aerosol performance of spray-dried powders of an anti-IgE humanized monoclonal antibody. Methods. Protein aggregation of spray-dried powders stored at various temperature and relative humidity conditions was assayed by size exclusion chromatography and sodium dodecyl sulfate polyacrylamide gel electrophoresis. Protein glycation was determined by isoelectric focusing and affinity chromatography. Crystallization was examined by X-ray powder diffraction. Aerosol performance was assessed as the fine particle fraction (FPF) of the powders blended with coarse carrier lactose, and was determined using a multiple stage liquid impinger. Results. Soluble protein aggregation consisting of non-covalent and disulfide-linked covalent dimers and trimers occurred during storage. Aggregate was minimized by formulation with trehalose at or above a molar ratio in the range of 300:1 to 500:1 (excipient:protein). However, the powders were excessively cohesive and unsuitable for aerosol administration. Lactose had a similar stabilizing effect, and the powders exhibited acceptable aerosol performance, but protein glycation was observed during storage. The addition of mannitol also reduced aggregation, while maintaining the FPF, but only up to a molar ratio of 200:1. Further increased mannitol resulted in crystallization, which had a detrimental effect on protein stability and aerosol performance. Conclusions. Protein stability was improved by formulation with carbohydrate. However, a balance must be achieved between the addition of enough stabilizer to improve protein biochemical stability without compromising blended powder aerosol performance.

5/AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011922173 BIOSIS NO.: 199900181833
Protein inhalation powders: Spray drying vs spray freeze drying
AUTHOR: Maa Yuh-Fun (Reprint); Nguyen Phuong-Anh; Sweeney Theresa; Shire Steven J; Hsu Chung C
AUTHOR ADDRESS: Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 16 (2): p249-254 Feb., 1999
1999
MEDIUM: print
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. To develop a new technique, spray freeze drying, for preparing protein aerosol powders. Also, to compare the spray freeze-dried powders with spray-dried powders in terms of physical properties and aerosol performance. Methods. Protein powders were characterized using particle size analysis, thermogravimetric analysis, scanning electron microscopy, X-ray powder diffractometry, and specific surface area measurement. Aerosol performance of the powders was evaluated after blending with lactose carriers using a multi-stage liquid impinger or an Anderson cascade impactor. Two recombinant therapeutic proteins currently used for treating respiratory tract-related diseases, deoxyribonuclase (rhDNase) and anti-IgE monoclonal antibody (anti-IgE MAb), were employed and formulated with different carbohydrate

excipients. Results. Through the same atomization but the different drying process, spray drying (SD) produced small (apprx3 mum), dense particles, but SFD resulted in large (apprx8-10 mum), porous particles. The fine particle fraction (FPF) of the spray freeze-dried powder was significantly better than that of the spray-dried powder, attributed to better aerodynamic properties. Powders collected from different stages of the cascade impactor were characterized, which confirmed the concept of aerodynamic particle size. Protein formulation played a major role in affecting the powder's aerosol performance, especially for the carbohydrate excipient of a high crystallization tendency. Conclusions. Spray freeze drying, as opposed to spray drying, produced protein particles with light and porous characteristics, which offered powders with superior aerosol performance due to favorable aerodynamic properties.

5/AB/16 (Item 16 from file: 5)

0011765572 BIOSIS NO.: 199900025232

Effect of mannitol crystallization on the stability and aerosol performance of a spray-dried pharmaceutical protein, recombinant humanized anti-IgE monoclonal antibody

AUTHOR: Costantino Henry R; Andya James D; Nguyen Phuong-Anh; Dasovich Nancy; Sweeney Theresa D; Shire Steven J; Hsu Chung C; Maa Yuh-Fun (Reprint)
AUTHOR ADDRESS: Pharmaceutical Res. and Development, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA**USA

JOURNAL: Journal of Pharmaceutical Sciences 87 (11): p1406-1411 Nov., 1998 1998
MEDIUM: print
ISSN: 0022-3549
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have examined the stability and aerosol performance of the pharmaceutical protein recombinant humanized anti-IgE monoclonal antibody (rhuMAbE25) spray dried with mannitol. The aerosol performance was measured by the fine particle fraction (FPF), and stability was assessed by the formation of soluble aggregates. When mannitol was added to the spray-dried rhuMAbE25 formulation, its ability to stabilize the protein leveled off above about 20% (w/w, dry basis). The FPF of the spray-dried formulations was stable during storage for rhuMAbE25 containing 10% and 20% mannitol, but the 30% formulation exhibited a dramatic decrease upon storage at both 5degreeC and 30degreeC, due to mannitol crystallization. We tested the addition of sodium phosphate to a 60:40 rhuMAbE25:mannitol (w:w) mixture, which otherwise crystallized upon spray drying and yielded a nonrespirable powder. The presence of sodium phosphate was successful in inhibiting mannitol crystallization upon spray drying and dramatically lowering the rate of solid-state aggregation. However, over long-term storage some crystallization was observed even for the phosphate-containing samples, concomitantly with increased particle size and decreased suitability for aerosol delivery. Therefore, the physical state of mannitol (i.e., amorphous or crystalline) plays a role both in maintaining protein stability and providing suitable aerosol performance when used as an excipient for spray-dried powders. Agents which retard mannitol crystallization, e.g., sodium phosphate, may be useful in extending the utility of mannitol as an excipient in spray-dried protein

formulations.

5/AB/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011652395 BIOSIS NO.: 199800446642
Fourier-transform infrared spectroscopic investigation of the secondary structure of aqueous and dried recombinant human deoxyribonuclease I
AUTHOR: Costantino Henry R (Reprint); Chen Bei; Griebenow Kai; Hsu Chung C; Shire Steve J
AUTHOR ADDRESS: Alkermes Inc., 64 Sidney St., Cambridge, MA 02139, USA**USA
JOURNAL: Pharmacy and Pharmacology Communications 4 (8): p391-395 Aug., 1998 1998
MEDIUM: print
ISSN: 1460-8081
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The secondary structure of aqueous and dried recombinant deoxyribonuclease I (rhDNase I) was studied by Fourier-transform infrared (FTIR) spectroscopy. The second derivative spectra for the amide I region, and also Gaussian curve-fitted original amide III spectra were examined. From the solution spectra, we discerned a mixed alpha/beta-composition, consistent with the native secondary structure determined by X-ray crystallography. Upon freeze drying, the amide 1 second derivative showed an increased absorbance at about 1691 cm-1, probably due to increased intermolecular beta-sheet formation. Gaussian curve-fitting of the amide III spectra also revealed an increase in beta-sheets (exhibiting absorbance at 1220-1237 cm-1), and some decrease in the alpha-helix content, a common occurrence for proteins upon drying. In addition, we tested several methodologies for preparation of solid rhDNase I samples (including transmission through the solid pressed directly between CaF2 windows) to confirm that the structural alteration was not a result of the conditions used in generating the spectra.

5/AB/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011482193 BIOSIS NO.: 199800276440
Effect of spray drying and subsequent processing conditions on residual moisture content and physical/biochemical stability of protein inhalation powders
AUTHOR: Maa Yuh-Fun (Reprint); Nguyen Phuong-Anh; Andya James D; Dasovich Nancy; Sweeney Theresa D; Shire Steven J; Hsu Chung C
AUTHOR ADDRESS: Pharm. Res. Dev., Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 15 (5): p768-775 May, 1998 1998
MEDIUM: print
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. To understand the effect of spray drying and powder

processing environments on the residual moisture content and aerosol performance of inhalation protein powders. Also, the long-term effect of storage conditions on the powder's physical and biochemical stability was presented. Methods. Excipient-free as well as mannitol-formulated powders of a humanized monoclonal antibody (anti-IgE) and recombinant human deoxyribonuclease (rhDNase) were prepared using a Buchi 190 model spray dryer. Residual moisture content and moisture uptake behavior of the powder were measured using thermal gravimetric analysis and gravimetric moisture sorption isotherm, respectively. Protein aggregation, the primary degradation product observed upon storage, was determined by size-exclusion HPLC. Aerosol performance of the dry powders was evaluated after blending with lactose carriers using a multi-stage liquid impinger (MSLI). Results. Spray-dried powders with a moisture level (apprx3%) equivalent to the freeze-dried materials could only be achieved using high-temperature spray-drying conditions, which were not favorable to large-scale manufacturing, or subsequent vacuum drying. These dry powders would equilibrate with the subsequent processing and storage environments regardless of the manufacturing condition. As long as the relative humidity of air during processing and storage was lower than 50%, powders maintained their aerosol performance (fine particle fraction). However, powders stored under drier conditions exhibited better long-term protein biochemical stability. Conclusions. Manufacturing, powder processing, and storage environments affected powder's residual moisture level in a reversible fashion. Therefore, the storage condition determined powder's overall stability, but residual moisture had a greater impact on protein chemical stability than on powder physical stability.

5/AB/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011310793 BIOSIS NO.: 199800105040
Determination of the average molecular weights of antibody and its complexes in serum using a preparative centrifuge
AUTHOR: Liou Jun; Reitz Barbara; Fox Judy; Shire Steve J
AUTHOR ADDRESS: Pharm R and D and Metabolism, Genenetch Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 14 (11 SUPPL.): pS348 Nov., 1997 1997
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Boston, Massachusetts, USA November 2-6, 1997; 19971102
SPONSOR: American Association of Pharmaceutical Scientists
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/AB/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011310441 BIOSIS NO.: 199800104688
The effect of formulation excipients and relative humidity on protein stability following storage and aerosol performance of spray dried powders of the anti-IgE humanized monoclonal antibody
AUTHOR: Andya James D; Nguyen Phuong-Anh; Maa Yuh-Fun; Dasovich Nancy;

Sweeney Theresa D; Hsu Chung C; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Res. Dev., Genetech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 14 (11 SUPPL.): pS217 Nov., 1997 1997
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Boston, Massachusetts, USA November 2-6, 1997; 19971102
SPONSOR: American Association of Pharmaceutical Scientists
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011180770 BIOSIS NO.: 199799814830
Interaction of human IgE with soluble forms of IgE high affinity receptors
AUTHOR: Liu Jun (Reprint); Ruppel Jane; Shire Steven J
AUTHOR ADDRESS: Dep. Pharm. Res. Dev., Genentech Inc., S. San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 14 (10): p1388-1393 1997 1997
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. Interaction of human IgE with its high affinity receptor (Fc-epsilon-RI) on mast cells and basophils is art important step for initiating IgE mediated immune responses. To characterize the IgE and Fc-epsilon-RI interaction, we investigated this interaction in terms of stoichiometry and binding affinity in solution. The binding of IgE and IgE Fc-epsilon-RI alpha chain, the extracellular portion of IgE high affinity receptor (sFc-epsilon-RI-alpha) was compared with the binding of IgE and IgE immunoadhesin (Fc-epsilon-RI-alpha-IgG). Methods. The interaction was characterized by analytical ultracentrifugation, size exclusion chromatography, light scattering and ELISA. Results. We show that the sFc-epsilon-RI-alpha is only able to bind to one IgE, while the immunoadhesin can bind to two IgE. The interaction between IgE and Fc-epsilon-RI is very strong. Both forms of soluble receptors have similar intrinsic binding affinity with IgE. Conclusions. Both soluble receptors (Fc-epsilon-RI-alpha-IgG and sFc-epsilon-RI-alpha) can block the binding of IgE to its high affinity receptors on cell surface. The Fc-epsilon-RI-alpha-IgG is a better IgE binding protein than sFc-epsilon-R-alpha at physio logical relevant conditions. A humanized anti-IgE monoclonal antibody, rhuMAb E25 that also can block the binding of IgE to its high affinity receptors appears to bind to IgE at slightly different regions or in a different manner as the soluble forms of IgE receptors.

5/AB/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010836315 BIOSIS NO.: 199799470375

IL-8 single-chain homodimers and heterodimers: Interactions with the chemokine receptors CXCR1, CXCR2, and DARC

AUTHOR: Leong Steven R; Lowman Henry B (Reprint); Liu Jun; Shire Steven; Deforge Laura E; Gillece-Castro Beth L; McDowell Robert; Hebert Caroline A
AUTHOR ADDRESS: Dep. Protein Eng., Genentech Inc., 460 Point San Bruno Blvd., South Francisco, CA 94080, USA**USA
JOURNAL: Protein Science 6 (3): p609-617 1997 1997
ISSN: 0961-8368
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Covalent single-chain dimers of the chemokine interleukin-8 (IL-8) have been designed to mimic the dimeric form of IL-8 in solution and facilitate the production of heterodimer variants of IL-8. Physical studies indicated that use of a simple peptide linker to join two subunits, while allowing receptor binding and activation, led to self-association of the tethered dimers. However, addition of a single disulfide crosslink between the tethered subunits prevented this multimer from forming, yielding a species of dimer molecular weight. Crosslinked single-chain dimers bind to both IL-8 neutrophil receptors CXCR1 and CXCR2 as well as to DARC, as does a double disulfide-linked dimer with no peptide linker. In addition, neutrophil response to these dimers as measured by chemotaxis beta-glucuronidase release is similar to that elicited by wild-type IL-8, providing evidence that the dissociation of the dimeric species is not required for these biologically relevant activities. Finally, through construction of single-chain heterodimer mutants, we show that only the first subunit's ELR motif is functional in the single-chain variants.

5/AB/23 (Item 23 from file: 5)

0010836314 BIOSIS NO.: 199799470374

Monomeric variants of IL-8: Effects of side chain substitutions and solution conditions upon dimer formation

AUTHOR: Lowman Henry B (Reprint); Fairbrother Wayne J; Slagle Paul H; Kabakoff Rhona; Liu Jun; Shire Steven; Hebert Caroline A
AUTHOR ADDRESS: Dep. Protein Engineering, Genentech Inc., 460 Point San Bruno Blvd., South San Francisco, CA 94080, USA**USA
JOURNAL: Protein Science 6 (3): p598-608 1997 1997
ISSN: 0961-8368
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: IL-8 dimers have been observed in NMR and X-ray structures of the protein. We have engineered IL-8 monomers by mutations of residues throughout the dimer interface, which introduce hindrance determinants to dimerization. These IL-8 variants are shown by NMR to have wild-type monomer folding, but by ultracentrifugation to have a range of dimerization constants from mu-M to mM, as compared with a dimerization constant of about 10 mu-M for wild-type IL-8, under physiological salt and temperature conditions. The monomeric variants of IL-8 bind the erythrocyte chemokine receptor DARC, as well as the neutrophil IL-8 receptors CXCR1 and CXCR2 with affinities similar to that of wild-type IL-8. In addition, the monomeric variants were shown to have agonist

activity, with similar potency to wild-type, in both Ca-2+-flux assays on CXCR1 and CXCR2 transfected cells, and in chemotaxis assays on neutrophils. Thus, these variants confirm that monomeric IL-8 is functionally equivalent to wild-type in in vitro assays. We have also investigated the effects of various solution conditions upon IL-8 dimer formation using analytical ultracentrifugation. At salt concentrations, temperatures, and pH conditions lower than physiological, the dimerization affinity of IL-8 is greatly enhanced. This suggests that, under some conditions, IL-8 dimer formation may occur at concentrations of IL-8 considerably lower than 10 mu-M, with consequences in vivo that are yet to be determined.

5/AB/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010806664 BIOSIS NO.: 199799440724
Characterization of truncated forms of human tissue factor-surfactant mixed micelles by analytical ultracentrifugation and EPR spectroscopy
AUTHOR: Cipolla David (Reprint); Shire Steven; Liu Jun; Bam Narendra; Jones Latoya S; Randolph Theodore W
AUTHOR ADDRESS: Aradigm Corp., Hayward, CA 94545, USA**USA
JOURNAL: Biophysical Journal 72 (2 PART 2): pA79 1997 1997
CONFERENCE/MEETING: 41st Annual Meeting of the Biophysical Society New Orleans, Louisiana, USA March 2-6, 1997; 19970302
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/AB/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010671993 BIOSIS NO.: 199799306053
Fast determination of the relative binding activity of rhuMAb E25 with optical biosensor
AUTHOR: Liu Jun; Gray Rebecca; Shire Steve J
AUTHOR ADDRESS: Pharm. R and D, Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.): pS102 1996 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996; 19961027
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010671992 BIOSIS NO.: 199799306052
Effect of Ca-2+ on the stability of DNase in phosphate and MES buffer
AUTHOR: Chen Bei (Reprint); Liu Jun; Shire Steve
AUTHOR ADDRESS: Pharmaceutical R and D, Genentech Inc., South San

Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.): pS102 1996 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996; 19961027
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010671897 BIOSIS NO.: 199799305957
The effect of sugars and buffer excipients on the stabilization of a lyophilized formulation for an anti-IgE humanized monoclonal antibody
AUTHOR: Andya James; Wu Sylvia; Hsu Chung; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Research Development, Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.): pS78 1996 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996; 19961027
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/28 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010341605 BIOSIS NO.: 199698809438
Analysis of protein interactions by analytical ultracentrifugation
AUTHOR: Shire Steven J
AUTHOR ADDRESS: Pharm. Res. Dev. Dep., Genentech Inc., S. San Francisco, CA 94080, USA**USA
JOURNAL: Abstracts of Papers American Chemical Society 211 (1-2): pBIOT 201 1996 1996
CONFERENCE/MEETING: 211th American Chemical Society National Meeting New Orleans, Louisiana, USA March 24-28, 1996; 19960324
ISSN: 0065-7727
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/29 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010107307 BIOSIS NO.: 199698575140
A novel solution based receptor inhibition assay to evaluate the interaction of anti-IgE monoclonal antibody and its Fab mutant to IgE
AUTHOR: Liu Jun; Shire Steven J
AUTHOR ADDRESS: Pharm R D, Genentech Inc., South San Francisco, CA 94080, USA**USA

JOURNAL: Pharmaceutical Research (New York) 12 (9 SUPPL.): pS96 1995 1995
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Miami Beach, Florida, USA November 5-9, 1995; 19951105
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/AB/30 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010048867 BIOSIS NO.: 199598516700
Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE
AUTHOR: Liu Jun; Lester Philip; Builder Stuart; Shire Steven J (Reprint)
AUTHOR ADDRESS: Pharm. Res. Dev., Genentech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Biochemistry 34 (33): p10474-10482 1995 1995
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The interaction of human IgE with high-affinity IgE F-c receptors on cells of the immune system plays an essential role in the type I hypersensitivity reaction. A proposed therapy is to use an anti-IgE monoclonal antibody to block the binding of IgE to its high-affinity receptor on mast cells and basophils, thus preventing subsequent release of the inflammatory agents after exposure to allergen. We report here the solution characteristics of immune complexes formed by a humanized anti-IgE monoclonal antibody (rhuMAb E25) and IgE using sedimentation analysis and size exclusion chromatography. We demonstrate that the rhuMAb E25 is able to form a variety of complexes with IgE at different molar ratios. The largest complex was identified by sedimentation equilibrium analysis as a heterohexamer with very high stability. The intermediate complex formed when one of the interacting components is in large molar excess appears to have a trimeric structure. The high-affinity interaction of rhuMAb E25 and IgE has also been confirmed. Furthermore, by using hydrodynamic modeling, we show that the largest complex may be represented by a cyclic structure.

5/AB/31 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009686254 BIOSIS NO.: 199598154087
Self-association IL-8 and its mutants: Effects of ionic strength and pH
AUTHOR: Liu Jun (Reprint); Lowman Henry B; Hebert Caroline A; Shire Steven J
AUTHOR ADDRESS: Dep. Pharm. R and D, Protein Eng. Immunol., Genentech Inc., 460 Pt. San Bruno Blvd., South San Francisco, CA 94080, USA**USA
JOURNAL: Biophysical Journal 68 (2 PART 2): pA410 1995 1995
CONFERENCE/MEETING: 39th Annual Meeting of the Biophysical Society San Francisco, California, USA February 12-16, 1995; 19950212
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Citation
LANGUAGE: English

5/AB/32 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009552001 BIOSIS NO.: 199598019834
Formulation Development of the Anti-p185-HER2 Humanized Monoclonal Antibody
AUTHOR: Andya James; Gray Rebecca; Shire Steven J
AUTHOR ADDRESS: Pharm. R and D Genentech Inc., S. San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 11 (10 SUPPL.): pS86 1994 1994
CONFERENCE/MEETING: Ninth Annual Meeting of the American Association of Pharmaceutical Scientists San Diego, California, USA November 6-10, 1994; 19941106
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/AB/33 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009551961 BIOSIS NO.: 199598019794
Determination of protein concentration by improved optical methods
AUTHOR: Gray Rebecca (Reprint); Stern Alan (Reprint); Bewley Thomas A (Reprint); Voelker Paul; McRorie Don; Liu Jun (Reprint); Shire Steven J (Reprint)
AUTHOR ADDRESS: Genetech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 11 (10 SUPPL.): pS76 1994 1994
CONFERENCE/MEETING: Ninth Annual Meeting of the American Association of Pharmaceutical Scientists San Diego, California, USA November 6-10, 1994; 19941106
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/AB/34 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009551954 BIOSIS NO.: 199598019787
Thermodynamic analysis of immune complex formation by humanized anti-IgE antibody and IgE
AUTHOR: Liu Jun; Lester Philip; Builder Stuart; Shire Steven
AUTHOR ADDRESS: Pharm R and D Process Sci., Genenetech Inc., South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 11 (10 SUPPL.): pS74 1994 1994
CONFERENCE/MEETING: Ninth Annual Meeting of the American Association of Pharmaceutical Scientists San Diego, California, USA November 6-10, 1994; 19941106
ISSN: 0724-8741
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation

LANGUAGE: English

5/AB/35 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009337200 BIOSIS NO.: 199497358485
TRAP, the trp RNA-binding attenuation protein of Bacillus subtilis, is a multisubunit complex that appears to recognize G/UAG repeats in the trpEDCFBA and trpG transcripts
AUTHOR: Babitzke Paul; Stults John T; Shire Steven J; Yanofsky Charles (Reprint)
AUTHOR ADDRESS: Dep. Biol. Sci., Stanford University Stanford, CA 94305, USA**USA
JOURNAL: Journal of Biological Chemistry 269 (24): p16597-16604 1994 1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A filter binding assay was developed to study interactions between purified TRAP, the trp RNA-binding attenuation protein of Bacillus subtilis, and trp specific transcripts. TRAP formed stable complexes with trpEDCFBA leader RNA, binding was L-tryptophan-dependent and was complete within 60 s. TRAP binds to a segment of the trp leader transcript that includes part of an RNA antiterminator structure. Binding to this segment allows formation of an RNA terminator structure, thereby promoting transcription termination. Using several trpEDCFBA leader deletion transcripts, we identified several closely spaced trinucleotide repeats (seven GAG and four UAG repeats) in the trp leader transcript that appeared to be required for TRAP binding. We also showed that TRAP binds to a segment of the trpG transcript that includes the trpG ribosome binding site; the nucleotide sequence of this segment contains several appropriately spaced trinucleotide repeats (seven GAG, one UAG, and one AAG). TRAP binding to the trpG transcript would block translation initiation. RNA footprint analysis confirmed interaction between TRAP and the trinucleotide repeats in the various transcripts. TRAP, in the presence or absence of L-tryptophan, appears to consist of 11 or 12 identical 8-kDa subunits. Our findings suggest that each tryptophan-activated TRAP subunit can bind one G/UAG repeat in a target transcript. Multiple protein-RNA interactions are required for stable association.

5/AB/36 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009223040 BIOSIS NO.: 199497244325
Characterization of aerosols of human recombinant deoxyribonuclease I (rhDNase) generated by jet nebulizers
AUTHOR: Cipolla David; Gonda Igor; Shire Steven J (Reprint)
AUTHOR ADDRESS: Pharmaceutical Research Development Dep., Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080, USA**USA
JOURNAL: Pharmaceutical Research (New York) 11 (4): p491-498 1994 1994
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recombinant human deoxyribonuclease I (rhDNase) is a new therapeutic agent developed to improve clearance of purulent sputum from the human airways. It is delivered by inhalation. Four jet nebulizers, T Up-Draft II (Hudson), Customized Respirgard II (Marquest), Acorn II (Marquest), and Airlife Misty (Baxter), were evaluated in vitro for their ability to deliver aerosols of rhDNase. The aerosols were generated from 2.5-mL aqueous solutions of rhDNase, at concentrations of either 1 or 4 mg/mL. In all experiments, the Pulmo-Aide Compressor (De Vilbiss) was used to supply the air to the nebulizers. Between 20 and 28% of the rhDNase dose initially placed in the nebulizers was delivered to the mouthpiece in the respirable range (1-6 mu-m). Evaluation of the rhDNase following nebulization in all four devices indicated that there was no loss in enzymatic activity and no increase in aggregation. Circular dichroism spectrophotometry indicated there was no change in either the secondary or the tertiary structure in rhDNase following nebulization. These results show that all four nebulizers are essentially equivalent in their ability to deliver respirable doses of rhDNase in an intact, fully active form. Changing the concentration of the solution in the nebulizer from 4 to 1 mg/mL rhDNase leads to a proportional reduction in the respirable dose delivered to the mouthpiece.

5/AB/37 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009184708 BIOSIS NO.: 199497205993
Formulation development of humanized monoclonal antibodies
AUTHOR: Shire Steven J; Gray Rebecca; Andya Jim
AUTHOR ADDRESS: Genentech Inc., 460 Pt. San Bruno Blvd., South San Francisco, CA 94080, USA**USA
JOURNAL: Abstracts of Papers American Chemical Society 207 (1-2): pBIOT 171 1994 1994
CONFERENCE/MEETING: 207th National Meeting of the American Chemical Society San Diego, California, USA March 13-17, 1994; 19940313
ISSN: 0065-7727
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/38 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009145657 BIOSIS NO.: 199497166942
Electron-microscopic and hydrodynamic characterization of recombinant apolipoprotein (a) and its association with LDL
AUTHOR: Phillips Martin L (Reprint); Lembertas Audra V; Schumaker Verne N; Lawn Richard M; Shire Steven J; Zioncheck Thomas F
AUTHOR ADDRESS: Dep. Chem. Biochem., Univ. Calif., 405 Hilgard Ave., Los Angeles, CA 90024, USA**USA
JOURNAL: Chemistry and Physics of Lipids 67-68 (0): p91-97 1994 1994
ISSN: 0009-3084
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A recombinant apo(a) containing 17 kringle 4 domains as well as

the kringle 5 and protease domains of apo(a) was characterized by hydrodynamic studies and electron microscopy. Recombinant apo(a) is a monomer in solution with a molecular weight of 325,000 by sedimentation equilibrium and 320,000 by sedimentation and diffusion, and it is a highly asymmetric molecule with a frictional ratio of 2.2. In the electron microscope recombinant apo(a) is visualized as a flexible chain of domains approximately 800 ANG long. Sedimentation velocity studies also demonstrate that when it is mixed with LDL, recombinant apo(a) reversibly forms an Lp(a)-like complex with a 1:1 stoichiometry; moreover, complex formation is inhibited by 6-amino hexanoic acid. Hydrodynamic modeling and electron microscopy suggest that only a small portion of the r-apo(a) molecule interacts with the LDL and the rest of the chain extends into solution. Preliminary studies indicate that recombinant apo(a) also binds mouse LDL.

5/AB/39 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009137412 BIOSIS NO.: 199497158697
The effect of a TYR fwdarw GLU mutation on the thermodynamics of heterologous and homologous association of light and heavy domains of the humanized 4D5 anti-p185-HER2 antibody
AUTHOR: Livingstone Jeff R (Reprint); Shire Steven J; Kelley Robert F
AUTHOR ADDRESS: FCRDC, NCI, Frederick, MD 21702, USA**USA
JOURNAL: Biophysical Journal 66 (2 PART 2): pA13 1994 1994
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the Biophysical Society New Orleans, Louisiana, USA March 6-10, 1994; 19940306
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/AB/40 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009077583 BIOSIS NO.: 199497098868
The development of stable protein formulations: A close look at protein aggregation, deamidation, and oxidation
AUTHOR: Cleland Jeffrey L; Powell Michael F (Reprint); Shire Steven J
AUTHOR ADDRESS: Genetech Inc., MS 10, 460 Pt. San Bruno Blvd., South San Francisco, CA 94080, USA**USA
JOURNAL: Critical Reviews in Therapeutic Drug Carrier Systems 10 (4): p 307-377 1993 1993
ISSN: 0743-4863
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

5/AB/41 (Item 41 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008838913 BIOSIS NO.: 199396003329
Biochemical characterization of the extracellular domain of the 75-kilodalton tumor necrosis factor receptor

AUTHOR: Pennica Diane (Reprint); Lam Van T; Weber Richard F; Kohr William J ; Basa Louisette J; Spellman Michael W; Ashkenazi Avi; Shire Steven J; Goeddel David V
AUTHOR ADDRESS: Dep. Molecular Biology, Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080, USA**USA
JOURNAL: Biochemistry 32 (12): p3131-3138 1993
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: An expression plasmid encoding the extracellular domain of the 75-kDa human tumor necrosis factor (TNF) type 2 receptor (TNF-R2) was constructed and used to generate a stable cell line secreting soluble TNF-R2(sTNF-R2). Purified sTNF-R2 was resolved by SDS-PAGE into one band of approximate M-r 43 000, consistent with a molecular weight of 36 000 +- 4800 obtained by sedimentation equilibrium analysis. The apparent molecular weight observed by gel filtration chromatography was approximately 136 000. Glycosylation analysis revealed that Asn-149 is fully glycosylated, while Asn-171 is incompletely glycosylated (apprx 50%), and that a proline-, serine-, and threonine-rich region (residues 175-234) contains O-linked carbohydrate structures. Scatchard analysis of (125I)TNF-alpha and (125I)TNF-beta binding to sTNF-R2 gave dissociation constants (K-d) of 0.3 and 0.75 nM, respectively, comparable to those observed for intact cell-surface TNF-R2. The sTNF-R2 was found to block the cytotoxicity of both TNF-alpha and TNF-beta in a murine L-M cell assay. The sizes of the sTNF-R2 cntdot TNF-alpha and sTNF-R2 cntdot TNF-beta complexes determined by gel filtration chromatography were approximately 322 and 204 kDa, respectively. The stoichiometry of the sTNF-R2 cntdot TNF-alpha and sTNF-R2 cntdot TNF-beta complexes was examined by size-exclusion chromatography, sedimentation equilibrium, and cross-linking. The data from these studies suggest that at least two molecules of sTNF-R2 can bind to a single TNF-alpha or TNF-beta trimer.

5/AB/42 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008837058 BIOSIS NO.: 199396001474
Physical properties of recombinant apolipoprotein(a) and its association with LDL to form an LP(a)-like complex
AUTHOR: Phillips Martin L; Lembertas Audra V; Schumaker Verne N (Reprint); Lawn Richard M; Shire Steven J; Zioncheck Thomas F
AUTHOR ADDRESS: Dep. Chem. Biochem., Univ. Calif., Los Angeles, CA 90024, USA**USA
JOURNAL: Biochemistry 32 (14): p3722-3728 1993
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recombinant apolipoprotein(a) has been studied by hydrodynamic techniques and electron microscopy. Recombinant apo(a) was primarily a monomer in solution with an S-0-20,w of 9.3 S, a D-20,w of 2.29 ficks, and a molecular weight of 325 000 from sedimentation equilibrium and 318 000 from combining the sedimentation and diffusion coefficients. A small amount, approximately 10%, of the recombinant apo(a) was present as a high molecular weight aggregate. The Stokes radius of the monomer, determined either from the diffusion coefficient or by combining the

sedimentation equilibrium data with the sedimentation velocity data, was 94 ANG . The frictional ratio was 2.2, suggesting a highly asymmetric or random coil structure. In the electron microscope, recombinant apolipoprotein(a) was visualized as a long, highly flexible chain of domains forming large, open coiled structures on the EM grid with contour lengths of about 800 ANG . Addition of 6-aminohexanoic acid at 50 mM, a concentration which should saturate the weak lysine binding sites, did not alter the sedimentation behavior. In vivo, apolipoprotein(a) is associated tightly with LDL to form a highly atherogenic lipoprotein, Lp(a). A single molecule of recombinant apo(a) also associated tightly with LDL to yield a 13.3-S Lp(a)-like complex. This complex dissociated upon the addition of 50 mM 6-aminohexanoic acid. A novel sucrose gradient centrifugation technique was employed to determine a dissociation constant for the reversible equilibrium between recombinant apo(a) and LDL; at physiological ionic strength the dissociation constant was 0.3 nM. Raising the salt concentration to 5 M NaBr caused the dissociation constant to increase to 500 nM. Hydrodynamic modeling suggests recombinant apo(a) made contact with the LDL through, at most, a few kringles, with the remainder of the molecule extending into solution. Our results suggest that, in addition to the apoB-apo(a) disulfide bond, strong noncovalent forces hold the Lp(a) molecule together. Furthermore, the bulk of apo(a) is extended away from the lipoprotein surface, where it may readily interact with other ligands.

5/AB/43 (Item 43 from file: 5)

0008736310 BIOSIS NO.: 199395038576

Quadruplex structure of d(G-3T-4G-3) stabilized by potassium or sodium is an asymmetric hairpin dimer

AUTHOR: Scaria P V; Shire Steven J; Shafer Richard H (Reprint)
AUTHOR ADDRESS: Dep. Pharmaceutical Chem., Sch. Pharm., Univ. Calif., San Francisco, Calif. 94143, USA**USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 89 (21): p10336-10340 1992
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ends of chromosomes contain repeats of guanine-rich sequences that can assume highly compact conformations and are presumed necessary for their biological role in chromosomal stabilization and association. We have investigated the conformational behavior of d(G-3T-4G-3) as a function of the addition of either KCl or NaCl, in the concentration range of 50-200 mM, by using a spectrum of physical techniques and conclude that these salts induce a quadruplex species composed of two strands, each in a hairpin conformation. When salt is added, a large positive signal appears near 290 nm in the CD spectra. UV thermal denaturation curves show a single concentration-dependent transition and provide data for quantitating the thermodynamics of quadruplex formation. In electrophoresis experiments, the quadruplex structure migrates as a single species and more rapidly than the unstructured single strand. NMR spectra in the presence of KCl or NaCl indicate that the structure formed is asymmetric. Equilibrium ultracentrifugation studies confirm that these quadruplexes are composed of two strands of d(G-3T-4G-3). Possible models for this structure are discussed.

5/AB/44 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008475498 BIOSIS NO.: 199344038394
Physical biochemistry of protein drugs
BOOK TITLE: Advances in Parenteral Sciences; Peptide and protein drug delivery
AUTHOR: Oeswein James Q; Shire Steven J
BOOK AUTHOR/EDITOR: Lee Vincent H L (Editor)
AUTHOR ADDRESS: Pharm. Res. Dev., Genentech Inc., South San Francisco, Calif, USA**USA
SERIES TITLE: Advances in Parenteral Sciences 4 p167-202 1991
BOOK PUBLISHER: Marcel Dekker, Inc., 270 Madison Avenue, New York, New York 10016, USA
Marcel Dekker, Inc., Basel, Switzerland
ISSN: 1041-004X ISBN: 0-8247-7896-0
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

5/AB/45 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

16420158 PMID: 15124199
Challenges in the development of high protein concentration formulations.
Shire Steven J; Shahrokh Zahra; Liu Jun
Department of Pharmaceutical R&D, Genentech, Inc., South San Francisco, California 94080, USA. steve shire@gene.com
Journal of pharmaceutical sciences (United States) Jun 2004, 93 (6) p1390-402, ISSN 0022-3549 Journal Code: 2985195R
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Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
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Development of formulations for protein drugs requiring high dosing (in the order of mg/kg) may become challenging for solubility limited proteins and for the subcutaneous (SC) route with <1.5 mL allowable administration volume that requires >100 mg/mL protein concentrations. Development of high protein concentration formulations also results in several manufacturing, stability, analytical, and delivery challenges. The high concentrations achieved by small scale approaches used in preformulation studies would have to be confirmed with manufacturing scale processes and with representative materials because of the lability of protein conformation and the propensity to interact with surfaces and solutes which render protein solubilities that are dependent on the process of concentrating. The concentration dependent degradation route of aggregation is the greatest challenge to developing protein formulations at these higher concentrations. In addition to the potential for nonnative protein aggregation and particulate formation, reversible self-association may occur, which contributes to properties such as viscosity that complicates delivery by injection. Higher viscosity also complicates manufacturing of high protein concentrations by filtration approaches. Chromatographic and electrophoretic assays may not accurately determine the non-covalent higher molecular weight forms because of the dilutions that are usually encountered with these techniques. Hence, techniques must be used that

allow for direct measurement in the formulation without substantial dilution of the protein. These challenges are summarized in this review. Copyright 2004 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 93:1390-1402, 2004

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Mechanisms of aggregate formation and carbohydrate excipient stabilization of lyophilized humanized monoclonal antibody formulations.
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The purpose of this study was to evaluate the mechanisms of aggregate formation and excipient stabilization in freeze-dried formulations of a recombinant humanized monoclonal antibody. Protein degradation was measured using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) and native size exclusion chromatography, and protein structure was studied using Fourier transform-infrared spectrometry and circular dichroism. The results showed that protein aggregates present following reconstitution were composed of native antibody structure and a reduced amount of free thiol when compared to protein monomer, which implied that intermolecular disulfides were involved in the aggregation mechanism. An excipient-free formulation resulted in reversible solid-state protein structural alteration and increased aggregation during storage. This correlated with dehydration to an extent that the amount of water was less than the estimated number of surface-accessible hydrogen-bonding sites on the protein. Improved native-like solid-state protein structure and reduced aggregation were obtained by formulation with enough carbohydrate to fulfill the hydrogen-bonding sites on the surface of the protein. Carbohydrate in excess of this concentration has less of an influence on protein aggregation. Reduced aggregation during storage was obtained by the addition of sufficient excipient to both stabilize solid-state protein structure and provide an environment that consisted of an amorphous glassy state matrix.
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Set	Items	Description
S1	621	E3-E12
S2	509	RD S1 (unique items)
S3	19	S2 AND ANTIBODY
S4	19	RD S3 (unique items)
S5	46	E1-E4